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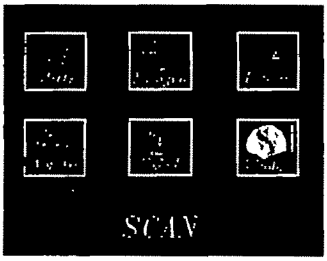

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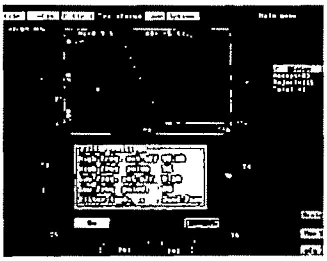

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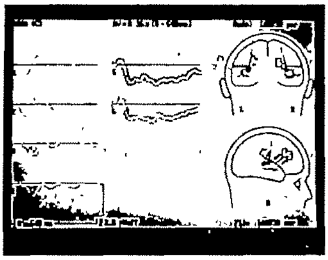

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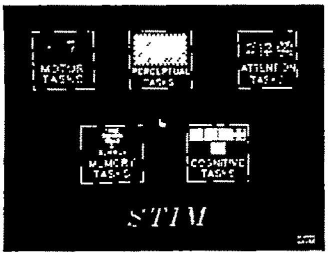

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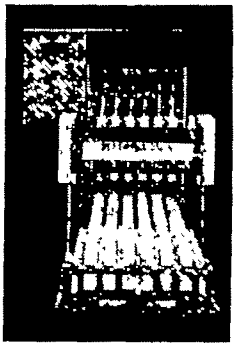

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THE ROLE OF THE RIGHT HEMISPHERE IN EMOTIONAL COMMUNICATION

by LEE XENAKIS BLONDER, DAWN BOWERS *and*
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SUMMARY

Previous research has established that patients with right hemisphere damage (RHD) are impaired in the comprehension of emotional prosody and facial expression. There are several explanations for this impairment. It may reflect defective acoustic and visuospatial analysis, disruption of nonverbal communicative representations, or a disturbance in the comprehension of emotional meaning. In order to examine these hypotheses, we asked RHD patients, left hemisphere damaged patients (LHD) and normal controls (NC) to judge the emotional content of sentences describing nonverbal expressions, and sentences describing emotional situations. We found that RHD subjects performed normally in their ability to infer the emotion conveyed by sentences describing situations. However, RHD patients were impaired in relation to both LHD and NC in the capacity to judge the emotional content of sentences depicting facial, prosodic, and gestural expressions, suggesting a disruption of nonverbal communicative representations.

INTRODUCTION

Neuropsychological studies of emotional communication have demonstrated that the right hemisphere (RH) plays a special role in decoding prosody in speech (Carmon and Nachshon, 1973; Heilman *et al.*, 1975; Tucker *et al.*, 1977; Ross and Mesulam, 1979; Ross, 1981; Ley and Bryden, 1982; Benowitz *et al.*, 1983; Heilman *et al.*, 1984; Bowers *et al.*, 1987) and facial expression (Ley and Bryden, 1979; Borod and Caron, 1980; Cicone *et al.*, 1980; DeKosky *et al.*, 1980; Benowitz *et al.*, 1983; Natale *et al.*, 1983; Etcoff, 1984*a, b*; Bowers *et al.*, 1985). Unlike neurobehavioural models of linguistic comprehension, however, the processing systems that underlie nonverbal communication of emotions have not been well elucidated. There remain several mechanisms by which prosodic and facial comprehension deficits may be explained.

At the most fundamental level, prosodic and facial comprehension disorders associated with right hemisphere damage (RHD) may reflect RH specialization in processing the complex visuospatial and acoustic stimuli in which the emotional message is embedded, rather than RH superiority in the interpretation of emotional signals per se. In particular, prosody is composed of fluctuations in fundamental frequency and amplitude over the duration of an utterance. In isolation from speech, these acoustic parameters are mediated by RH mechanisms (Milner, 1962; Sidtis, 1980). Likewise, perception of facial emotions involves complex visuospatial processing, also a function of the RH. This hypothesis is further supported by studies showing impaired performance by RHD patients on simple

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prosodic discrimination tasks (Tucker *et al.*, 1977; Weintraub *et al.*, 1981) and facial discrimination tasks (DeKosky *et al.*, 1980), neither of which require emotional judgements. Sergent and Bindra (1981) and Bruyer and Stroot (1984) provided evidence that the RH contributes to the discrimination of faces while the left hemisphere (LH) dominates in the recognition of faces, further supporting the notion that a particular type of holistic visuospatial processing underlies facial discrimination by the right hemisphere.

At a more specialized level, receptive prosodic and facial communicative abnormalities may result from damage to representations of species-typical facial expression prosodic contours, and gestures resident in the RH. These *nonverbal* representations of emotion would encode the facial, prosodic, and gestural configuration of specific nonverbal signs as well as their meaning in social communication. Support for this hypothesis is given by research indicating that the RH is particularly involved in judging the emotional significance of prosody and facial expression (Heilman *et al.*, 1975; Ley and Bryden, 1979; Ross and Mesulam, 1979; Borod and Caron, 1980; Cicone *et al.*, 1980; DeKosky *et al.*, 1980; Ross, 1981; Benowitz *et al.*, 1983; Natale *et al.*, 1983; Etcoff, 1984*b*; Heilman *et al.*, 1984; Bowers *et al.*, 1985, 1987). In particular, Bowers *et al.* (1985) found that deficits on tasks of facial affect identification shown by RHD patients exist over and above impairment in the discrimination of facial identity. Similarly, in tachistoscopic studies on normal individuals, Suberi and McKeever (1977) and Ley and Bryden (1979) found increased left visual field superiority in recognizing emotional versus neutral faces (*see* Silberman and Weingartner, 1986, for a review).

Finally, nonverbal communicative comprehension disorders may reflect a more generalized disturbance at the level of emotional understanding or knowledge. Studies involving hemisphere mediation of emotional language lend support to this hypothesis. For example, Wechsler (1973) reported that RHD patients have relatively more difficulty recalling emotional stories than nonemotional stories. In a series of experiments with normal subjects, Ley (1980) and Ley and Bryden (1983) found that the presentation of emotional words during a list learning task selectively improved memory of stimuli directed to the right hemisphere. In a tachistoscopic study involving the capacity of the normal left versus RH to identify emotional words, Graves *et al.* (1981) found a left visual field advantage in males but not females. Landis *et al.* (1982) showed preferential reading and writing of emotion words compared with nonemotional words by aphasics, suggesting that the RH houses a lexical representation of emotions. In contrast, Etcoff (1984*a*) compared similarity judgements of photographs of facial affect with those of emotion words and found that RHD subjects were impaired on the former task but not the latter, suggesting a perceptual rather than a conceptual defect in emotion processing. Recent research suggests that RHD patients have difficulty integrating contextual cues that are necessary for the appreciation of verbal and pictorial humour, metaphor and connotative meaning. These patients are prone to literal interpretations and inappropriate affective responses (Gardner and Denes, 1973; Gardner *et al.*, 1975; Winner and Gardner, 1977; Wapner *et al.*, 1981; Brownell *et al.*, 1983; Gardner *et al.*, 1983; Foldi, 1987).

The objective of the present study was to determine further whether impairments in the comprehension of prosody and facial expression associated with RHD reflect (1) perceptual disturbances limited to acoustic and visuospatial presentation of prosodic and facial stimuli, (2) the inability to infer the mean of nonverbal communicative signals regardless of channel of presentation, or (3) a lack of understanding of the emotional significance of events, irrespective of linguistic versus paralinguistic delivery. If RHD patients are solely impaired on receptive tasks involving facial and prosodic stimuli, then we would conclude that the emotional communicative disorder is perceptual in nature, that is, related to RH specialization in interpreting the complex acoustic and visuospatial signals. Alternatively, if RHD patients also have difficulty interpreting the emotional significance of verbal descriptions of prosodic, facial, and gestural signals, but are able to interpret the meaning of emotional sentences, then we would conclude that the RH contains specialized representations of nonverbal communicative expressions. Finally, if RHD patients are impaired in the ability to infer the emotional meaning of sentences which are devoid of nonverbal descriptors, this would provide evidence that these patients have a more deeply rooted derangement in their knowledge of emotion.

SUBJECTS

A total of 30 right-handed patients (29 men, 1 woman) were recruited from the neurology and orthopaedic services at the University of Florida Shands Teaching Hospital and the Veterans Administration Medical Center, Gainesville, Florida. These included (1) 10 patients (all males) with cerebral infarctions limited to the right hemisphere (RHD), (2) 10 patients (9 males, 1 female) with cerebral infarctions confined to the left hemisphere (LHD), and (3) 10 patients (all males) with orthopaedic disease and no history of illness involving the central nervous system (NC). None of the participants had a history of psychiatric or neurological disease other than stroke. The three groups did not differ in age (mean(±SD), RHD: 64.1 yrs (5.3); LHD: 59.6 (9.6); NC: 63.2 (4.7)), or yrs of education (RHD: 12.3 (3.8); LHD: 13.4 (1.8); NC: 12.7 (2.1)). The stroke patients did not differ in months since stroke (RHD: 40.7 (49); LHD: 55.7 (47.4)). All stroke patients had CT scans documenting the presence and location of the lesion. All lesions involved the cerebral cortex and/or adjacent subcortical regions. The characteristics of the patients are provided in Tables 1 and 2.

TABLE 1 DEMOGRAPHIC CHARACTERISTICS

	Age		*Education (yrs)*		*Months since CVA*	
Group	*Mean (SD)*	*Range*	*Mean (SD)*	*Range*	*Mean (SD)*	*Range*
RHD (n = 10)	64.1 (5.3)	52–70	12.3 (3.8)	5–18	40.7 (49.0)	1–159
LHD (n = 10)	59.6 (9.6)	45–72	13.4 (1.8)	9–15	55.7 (47.4)	1–135
NC (n = 10)	63.2 (4.7)	55–69	12.7 (2.1)	9–16		

METHODS

Task 1. Comprehension of emotional prosody and facial expression

In order to examine the nature of the receptive emotional disturbance in RHD patients, it is necessary first to establish that this particular sample has deficits at the level of facial and prosodic perception. We used the Florida Affect Battery—Revised to assess these functions. This battery consists of three major parts. Part 1 is made up of tests of facial discrimination, verbal labelling of facial expressions, and facial matching. Part 2 involves comprehension of emotional and nonemotional prosody, and Part 3 consists of cross-modal tasks in which the subject is required to match the emotion conveyed by facial expression with a corresponding prosodic contour. A more complete description of the subtests is provided below.

TABLE 2 PATIENT CHARACTERISTICS

Case/age (yrs)/sex	*Mos since CVA*	*CT lesion location**	*Clinical symptoms*		
			Hemiparesis	*Aphasia*	*Neglect*
1 72 M	135	L temporoparietal occipital	−	Wernicke	−
2 61 M	111	L frontotemporal parietal	+	Broca	−
3 55 M	179	L frontotemporal parietal occip. cingulate, insula	+	Broca	−
4 64 M	41	L frontal	+	Transcortical motor	−
5 45 M	72	L frontotemporal parietal, insula	+	Broca	−
7 72 M	84	L temporoparietal, insula	−	Broca (mild)	−
8 45 M	01	L temporoparietal	+	Anomia	−
9 52 F	09	L temporoparietal	−	Anomia	−
10 59 M	24	L frontal	+	Broca	−
12 63 M	02	L Temporal, insula	−	Anomia	−
13 67 M	05	R frontoparietal	+	−	+
14 52 M	76	R frontotemporal parietal, insula	+	−	−
15 61 M	09	R frontotemporal parietal, insula	+	−	+
16 70 M	159	R frontotemporal parietal	+	−	+
17 62 M	44	R temporoparietal	−	−	−
18 67 M	12	R parietal occipital	+	−	+
19 70 M	63	R parietal occipital	−	−	+
20 66 M	29	R frontotemporal parietal, insula	−	−	+
21 64 M	09	R occipital temporal	+	−	−
22 62 M	01	R frontotemporal parietal	+	−	+

* Localizations based on templates of Matsui and Hirano (1978) and Damasio and Damasio (1990).

Test construction

The facial stimuli used in the facial perception subtests consisted of 35 mm black and white close-up photographs of female faces in full view. None of the posers were professional actresses. Posers were simply asked to look happy, sad, angry, frightened, or neutral. The original set of emotional facial photographs was rated by 18 normal individuals, less than 40 yrs old, who had no history of neurological or major psychiatric disease. Only those facial photographs which achieved an interrater agreement of 80% or greater with respect to the intended emotion were included. The test photographs are approximately 2×3 inches in size and when more than one is presented simultaneously, they are arranged on a white card in a vertical array in order to minimize the possible confounding effects of hemispatial neglect. In each subtest, stimuli are presented in random order. All subtests of the battery were scored as percentage correct.

Subtest 1. Discrimination of facial identity. Subjects were shown 20 pairs of photographs of females each with neutral facial expression. In each photograph, the hair was covered by a surgical cap in order to reduce nonfacial cues to identity. The subject was asked to determine whether each pair of photographs represents the same person or 2 different people.

Subtest 2. Discrimination of facial emotion. Subjects were shown 20 pairs of photographs of females and asked to determine whether the actresses were expressing the same emotion or 2 different emotions. The identity of the actresses in any given pair was different.

Subtest 3. Name the emotion on the face. Subjects were shown photographs, one at a time, of 5 actresses expressing happiness, sadness, anger, fear, or neutrality, for a total of 20 trials. The subject was provided with a card on which the 5 emotion words were printed and asked to select from these possibilities the one which best characterized the expression on the target face

Subtest 4. Point to the emotional face. This subtest consists of 5 photographs per card of a single actress expressing each of the 5 emotions. For each set of 5 photographs, the subject was told an emotion and asked to point to the photograph that best expressed it. There were 20 trials.

Subtest 5. Match the emotional faces. Subjects were shown a small card containing a photograph of 1 emotional face and a larger card with photographs of 5 different actresses each expressing one of the

5 emotions. The subject was asked to match the emotional expression on the small card to a face on the larger card that was expressing the same emotion. There were 20 test trials.

Prosodic comprehension subtests

The prosody tests were designed to complement the facial perception tasks with respect to dimensions measured The stimuli for all prosodic subtests consisted of a set of neutral content simple sentences (e.g., 'The shoes are in the closet'; 'The boy went to the store') read by one of the investigators (D.B.) using various nonemotional and emotional intonation contours. The same stimulus sentences were used throughout the Prosody Battery. The sentences were audiotaped on a Revox B 77 reel-to-reel stereo tape recorder. The subject and the examiner simultaneously listened to the sentences through headphones.

Subtest 1. Discrimination of neutral prosody. Subjects listened to an audiotape of 16 pairs of simple sentences, spoken with question intonation (pitch final rise) or statement intonation (pitch final fall). The subject was asked whether the prosody ('tone of voice') was the same or different across the 2 sentences.

Subtest 2. Discrimination of emotional prosody. Subjects were asked to listen to 20 pairs of simple sentences and state whether the emotional prosody was the same across the 2 sentences or different.

Subtest 3. Name the emotional prosody. Subjects were asked to listen to an audiotape of 20 stimulus sentences and select, from a card on which happy, sad, angry, frightened, and neutral emotion terms were printed, and match the emotion which best characterized the intonation in the stimulus voice.

Subtest 4. Match the emotional prosody to the emotional face. Subjects were shown a card with 3 photographs of the same actress expressing 3 different emotions. At the same time, the subject listened to an audiotaped sentence reflecting 1 of the 5 emotions per trial. The subject was asked to point to the facial photograph that best matched the emotion expressed through tone of voice. There were 20 items in this task.

Subtest 5. Match the emotional face to the emotional prosody. Subjects were shown a card with a photograph of 1 emotional face and asked to select from 3 prerecorded sentences expressing 3 different emotional prosodic contours the one which best corresponded to the facial emotion. Because this test entails some memory load, each set of 3 sentences was repeated a second time. There were 20 items in this test.

Task 2. Verbal descriptors of nonverbal expressions

The purpose of this task was to determine whether RHD patients can comprehend nonverbal expressions of emotion when communicated by verbal descriptions. We therefore constructed a test in which happy, sad, angry, frightened, and neutral emotions are conveyed by verbal descriptors of facial, prosodic, and gestural signals. The sentences ranged from 2 to 6 words in length. Some examples are 'He scowled', 'She smiled', 'Tears fell from her eyes', 'He coughed', 'He spoke quickly and breathlessly', 'She laughed', 'He shook his fist', 'He bolted'. We designed this experiment to determine whether the paralinguistic deficit associated with RHD is solely related to the acoustic and visuospatial nature of these communicative signals, or whether RHD patients are impaired at the level of nonverbal communicative representations. If the deficit is acoustic or visuospatial in nature, then we would expect RHD patients to perform abnormally on receptive facial and prosody tasks (Task 1) and normally on this task. However, if RHD causes a disturbance at the level of nonverbal communicative representations, then we predict poor performance on both the prosody and facial perceptual tasks and this task.

The stimulus sentences used in this task were initially drawn from a pool of 91 sentences which were administered to a group of 18 neurologically and psychiatrically normal elderly controls. We selected from these a subset of items on which intersubject agreement equalled or exceeded 80%. The final test consisted of 56 stimulus sentences. We applied the Flesch-Kinkaid formula to this test to determine the approximate grade level required to read these sentences. This formula is used by the United States Department of Defense in producing manuals for the armed services. Grade level is based on average sentence length in words (ASL) and average number of syllables per word (ASW). According to the Flesch-Kinkaid formula (grade level = $(0.39 \times \text{ASL})+(11.8 \times \text{ASW}) = 15.59$) subjects require a first grade level of education in order to understand this test.

Procedures

Because many of our RHD patients had hemispatial neglect and visuospatial processing deficits and because some LHD patients had difficulty reading, the stimulus sentences were presented simultaneously in both auditory and visual modalities. In order to minimize the possible introduction of prosodic cues to emotion, the sentences were synthesized using DECtalk, a text-to-speech synthesizer manufactured by Digital Equipment Corporation (Maynard, MA). DECtalk produces artifically synthesized high quality speech in which the vocal contour of words and sentences follows the basic rules of English pronunciation and prosody. Because DECtalk does not understand word meaning, intonation and stress patterns are relatively regular across sentences, regardless of content. In addition, prosodic parameters such as rate and pitch range are preprogrammed, further limiting 'leakage' of meaning through the intonation channel. The order of sentence presentation was randomized and an audiotape of the synthesized sentences was made.

The audiotaped synthesized sentences were played on a stereo cassette tape deck to the subject who was seated at a table in a quiet room. In addition to hearing the sentences, subjects were provided with 5×7 inch cards on which each sentence was printed. They listened to and silently read each item simultaneously and responded by selecting, from a vertically arrayed multiple choice display of 5 emotion terms, the one which best characterized the emotional content of the sentence. There was a 10 s interval between each item and if a subject needed more time, the tape was paused. Before experimental testing, the subject heard an 'Introduction of DECtalk' tape to help familiarize him/her with the synthesized voice. Five practice items were given. The examiner recorded the patient's response on a score sheet and results were tabulated as percentage correct facial descriptors (e.g., 'She smiled'), percentage correct prosodic descriptors (e.g., 'He spoke quickly and breathlessly'), and percentage correct gestural descriptors (e.g., 'He shook his fist'). In total, there were 16 facial descriptors, 14 prosodic descriptors, and 26 gestural descriptors.

Task 3. Comprehension of emotional sentences

The purpose of Task 3 is to determine whether RHD patients can derive the emotional meaning of situations that are prototypically linked to specific emotions. In this task, the 5 emotions (happy, sad, angry, frightened, or neutral) are conveyed by sentences containing emotion words and verbal reference to emotionally charged situations. The principal difference between this task and Task 2 is that the sentences used in this task contain no words or phrases that describe facial, gestural, or prosodic signals. In comparing performance on these two tasks, we expected to discover whether (1) RHD patients have a disorder restricted to the interpretation of paralinguistic expressions, or (2) whether they manifest a more generalized disturbance in the interpretation of emotional events. If the deficit following RHD is specific to nonverbal signals of emotion rather than emotional knowledge in general, we expected abnormal performance on Tasks 1 and 2, and normal performance on this task.

Subjects were presented with a series of 75 statements, ranging from 5 to 19 words in length. For each emotion except neutral, sentences were created in which there were 3 levels of inferential complexity. In *Level 1* sentences, which we termed 'denotative', lexical items denoting the target emotion were included. For example, in the sentence 'You were delighted by the bonus', the word 'delighted' denotes happiness and these 2 emotion words (happy, delighted) may be used interchangeably. Additional information regarding emotion is provided by the term 'bonus', which is usually associated with positive emotion. In these Level 1 sentences, then, emotionality is conveyed by terms which are synonymous with 1 of the 5 response choices, and by contextual cues in the form of 'buzzwords' connotative of the particular emotion. We intended these sentences to provide the subject with the greatest amount of semantic and contextual cues to the emotion.

In *Level 2* sentences, no emotion words were used. Emotions were conveyed solely through contextual information and the use of 'buzzwords' or phrases which are associated with the particular emotion. For example, in the sentence 'It was the third anniversary of the death of your child', the word 'death', while not a synonym per se of sadness, usually evokes sadness or grief. Or, in the sentence 'You are complimented by your boss for your excellent work', the words 'complimented' and 'excellent' are usually associated with happiness. Thus we expected that Level 2 sentences would require the subject to exercise a greater degree of inferential emotional-linguistic processing than Level 1 sentences, in that he/she is no longer being told the emotion through the use of synonyms of the major emotion terms. We refer to these Level 2 sentences as 'connotative'.

Level 3 sentences are designed to require the highest level of inferential linguistic-emotional processing in that no emotion terms, buzzwords, or phrases connotative of particular emotions are used. Emotional meaning is conveyed through contextual cues and require the subject to comprehend the meaning of the sentence as a whole, and to infer from the situation described, which emotion she or he would feel. Some examples of Level 3 ('interpretative') sentences are 'After you drink the water, you see the sign'; 'Your house seems empty without her'; 'Your newly painted surface began to peel off'; 'Your team's ball went through the hoop with one second left to go in the game'.

The stimulus sentences used in this task were drawn from a pool of 151 sentences which had been administered to 18 normal elderly controls. The final task consisted of 75 sentences on which the normal elderly achieved 80% or higher agreement regarding the emotional content of the sentence. Of these 75 sentences, there were 15 in each of the five emotional categories. The happy, sad, angry, and frightened categories consisted of 5 items for each of 3 levels (denotative, connotative, interpretive). For neutral, there were 2 levels represented: 5 items in the denotative category and 10 in the connotative category. It proved impossible to create neutral sentences differentiated by the presence or absence of 'buzzwords'. As in the previous test, we subjected this test to the Flesch-Kinkaid readability formula and found that subjects require a fourth grade level of education in order to comprehend the test.

As in Task 2, the sentences used in this experiment were synthesized using DECtalk. The order of sentence presentation was randomized and an audiotape of the synthesized sentences was made. The audiotaped sentences were played on a stereo cassette tape deck to the subject who was seated at a table in a quiet room. In addition to hearing the sentences, subjects were provided with 5×7 inch cards on which each sentence was printed. Subjects listened to and silently read each item simultaneously and responded by selecting, from a vertically arrayed multiple choice display of 5 emotion terms, the one which best characterized the emotional content of the sentence. As in the previous test, there was a 10 s interval between each item and if a subject needed more time, the examiner paused the tape. Five practice items were given. The examiner recorded the patient's response on a score sheet and results were tabulated as percentage correct for each emotion by level of inferential complexity.

RESULTS

Task 1. Receptive facial and prosodic expression

The scores of percentage correct on the facial and prosodic comprehension subtests of the revised Florida Affect Battery were individually analysed using one-way analysis of variance (ANOVA) with lesion locus (RHD, LHD, NC) as the between-group factor. The Levene test was used to assess homogeneity of variance and when significant, an ANOVA without equal variance assumption was performed. When the individual ANOVAs were significant, t tests were performed to determine which groups differed. In cases where the variances were not homogeneous, we used the separate variance T. Otherwise, we report the *P* value associated with the pooled variance T.

Our results confirmed that this sample of RHD patients have difficulty perceiving facial and prosodic expression, thus replicating previous research. In particular, RHD patients were significantly impaired relative to LHD and NC subjects in the discrimination of facial identity, the discrimination of facial emotion, and matching facial emotions. Among the prosody tests, RHD patients were impaired relative to LHD and NC on discrimination of question and statement intonation, discrimination of emotional prosody, and naming the emotion conveyed by prosody. Finally, RHD patients were impaired relative to LHD and NC on both cross-modal tasks requiring subjects to associate emotional prosody correctly with emotional facial expressions. The LHD patients' performance was comparable to normals on all measures. The means and SDs on facial and prosodic perception tests are given in Table 3.

Task 2. Verbal descriptors of nonverbal expression

Subjects' responses on the Verbal Descriptors of Nonverbal Expressions task were recorded as percentage correct and analysed using a repeated measures ANOVA with lesion locus (RHD, LHD, NC) as the between-group factor and channel (face, voice, gesture) as the within-group factor. Results indicated a main effect of lesion locus, $F(2,27) = 7.19$, $P = 0.003$.

TABLE 3 MEANS AND SDs ON TASK 1 PERCEPTION OF FACIAL EXPRESSION AND PROSODY (FLORIDA AFFECT BATTERY—REVISED)

	RHD *(n = 10)*	*LHD* *(n = 10)*	*NC* *(n = 10)*	*Significance*
Facial identity discrimination	79.5 (15.4)	94.5 (7.3)	95.0 (5.3)	A B*
Facial emotion discrimination	68.0 (13.0)	81.5 (7.1)	90.5 (8.3)	A* B**
Name emotional face	80.0 (13.9)	84.5 (13.6)	89.5 (9.6)	n.s.
Point to emotional face	84.5 (15.5)	95.5 (6.4)	96.5 (4.7)	B
Match emotional face	65.5 (23.6)	85.5 (11.9)	91.5 (14.4)	A B*
Discriminate neutral prosody	80.1 (17.7)	89.4 (13.9)	97.6 (4.1)	B*
Discriminate emotional prosody	85.5 (15.7)	97.0 (6.3)	99.0 (2.1)	A B
Name emotional prosody	63.5 (18.0)	81.5 (11.6)	83.0 (12.1)	A* B*
Match prosody to faces	64.0 (19.4)	81.5 (15.1)	89.0 (9.9)	A B**
Match face to prosody	71.0 (17.5)	90.5 (6.4)	95.5 (7.3)	A* B*

A = RHD < LHD, $P < 0.05$; A* = RHD < LHD, $P < 0.01$, B = RHD < NC, $P < 0.05$, B* = RHD < NC, $P < 0.01$; B** = RHD < NC, $P < 0.001$.

Post hoc comparisons using Tukey's test revealed that RHD patients performed significantly worse than both LHD patients ($P < 0.05$) and NC ($P < 0.001$) in their ability to determine the mean of nonverbal signals depicted via verbal language. There was also a main effect of channel (face, prosody, gesture) (F(4,54) = 3.54, $P < 0.05$). Post hoc comparisons using Tukey's test revealed no significant pairwise differences. The means and SDs by channel of communication are provided in Table 4.

TABLE 4. MEANS AND SDs ON TASK 2 VERBAL DESCRIPTORS OF NONVERBAL EXPRESSIONS

	RHD *(n = 10)*	*LHD* *(n = 10)*	*NC* *(n = 10)*	*All subjects*
Facial descriptors	71.3 (15.8)	79.5 (11.4)	86.5 (9.8)	79.1
Prosodic descriptors	71.5 (15.2)	85.8 (10.2)	93.7 (7.7)	83.7
Gestural descriptors	78.9 (9.1)	84.5 (7.2)	87.1 (6.6)	83.6
Overall mean	73.9	83.2	89.1	82.1

Effect of lesion locus: F(2,27) = 7.19, $P < 0.003$.

Task 3. Comprehension of emotional sentences

For this task, scores were analysed using a repeated measures ANOVA with lesion locus (RHD, LHD, NC) as the between-group factor and level (denotative, connotative, interpretive) and emotions (happy, sad, angry, frightened) as within-group factors. Neutral items were excluded from this analysis because only two categories (denotative, connotative) were present.

There was no main effect of lesion locus (F(2,27) = 2.41, $P = 0.11$), indicating that, overall, the performance of the 3 patient groups (RHD, LHD, NC) was comparable. There was, however, a significant interaction between lesion locus and emotion (F(6,81) 2.51, $P = 0.03$). Post hoc contrasts, using Cicchetti's (1972) extension of Tukey's test to interaction tables (this solution is based on the number of unconfounded comparisons only), revealed that RHD patients performed significantly more accurately on happy statements than on angry statements. There were no differences, however, between the 3 diagnostic groups in performance by emotion. In spite of the lack of between-group differences, we examined overall tendencies of RHD and LHD groups to 'neutralize' negative sentences and make positive neutral sentences (i.e., err in the direction of making sentences more positive). We found that 46% of RHD patients' errors and 45% of LHD patients' errors displayed this pattern, suggesting no particular tendency as a function of hemisphere locus of lesion.

Our results also indicated a main effect of emotion, $F(3,81) = 8.20$, $P < 0.0001$. Post hoc contrasts using Tukey's test showed that overall, subjects performed less accurately on angry, sad, and frightened sentences than on happy ones ($P < 0.05$). The means and SDs by emotion are given in Table 5.

TABLE 5 MEANS AND SDs ON TASK 3 EMOTIONAL INFERENCE BY EMOTION

	RHD (*n* = *10*)	*LHD* (*n* = *10*)	*NC* (*n* = *10*)	*All subjects*
Happy sentences	96.7 (4.7)	92 7 (12 3)	95.3 (10.1)	94.9
Sad sentences	84.2 (19.1)	76.7 (22.6)	92.0 (14.9)	84.3
Angry sentences	76.0 (25.7)	87.3 (15.4)	91.3 (12.9)	84 9
Frightened sentences	78.0 (18.8)	82.0 (19.1)	90.7 (13.9)	83.6
Overall mean	83 7	84.7	92.3	86.9

Effect of emotion $F(3,81) = 8.20$, $P < 0.0001$, emotion×lesion locus: $F(6,81) = 2.51$, $P < 0.03$ (RHD angry < RHD happy, $P < 0.05$).

There was a main effect of level, $F(2,54) = 13.80$, $P < 0.0001$. A posteriori contrasts using the Tukey test revealed that participants performed more poorly on connotative than on interpretative statements ($P < 0.05$). There were no differences between denotative sentences and either of the other two levels. These results suggest that the assumptions underlying the construction of our questionnaire were only partially valid: interpretative items were more difficult than connotative items, but the presence of emotion words in denotative sentences did not increase subjects' accuracy. The group means and SDs by level of inferential complexity are given in Table 6.

There was also an interaction between level and emotion ($F(6,162) = 4.31$, $P < 0.0005$). Post hoc comparisons using Cicchetti's (1972) extension of the Tukey test showed that, within emotions, subjects performed more poorly on sad items that contained denotative terms (e.g., 'You were gloomy about being left behind') than they did on

TABLE 6 MEANS AND SDs ON TASK 3. EMOTIONAL INFERENCE BY LEVEL OF INFERENTIAL COMPLEXITY

	RHD (*n* = *10*)	*LHD* (*n* = *10*)	*NC* (*n* = *10*)	*All subjects*
Denotative sentences	82 0 (17 6)	82 0 (19.5)	94.0 (11.5)	86.0
Connotative sentences	89 5 (11.9)	91.5 (14 4)	95 0 (11 0)	92.0
Interpretative sentences	79 7 (18.5)	80.5 (17.6)	88.0 (16 5)	82.7
Overall mean	83.7	84.7	92 3	86.9

Effect of level: $F(2,54) = 13.80$, $P < 0.0001$.

sentences that contained words or phrases connotative of sadness (e.g., 'You are leaving your home town and all your friends'); they also performed more poorly on angry sentences containing no emotion terms or buzzwords (interpretative level) than on angry denotative and angry connotative items. Within level, subjects performed worse on denotative sentences conveying sadness than they did on denotative items conveying happiness. Likewise, they performed more poorly on both angry and frightened items requiring interpretation than on happy items requiring interpretation. There was no level by lesion locus interaction (F(4,54) = 1.03, $P = 0.40$) and no level by lesion locus by emotion interaction (F(12,162) = 1.41, $P = 0.17$).

In view of the literature suggesting that positive and negative emotions are organized differently in the two hemispheres (*see* Davidson, 1984, and Silberman and Weingartner, 1986, for reviews), we performed an ANOVA in which diagnosis (RHD, LHD, NC) was the between-group factor and valence (happy, sad) was the within-group factor. These was no effect of lesion locus (F(2,27) = 1.97, $P = 0.16$), but there was a main effect of valence, with participants performing more accurately on happy than on sad sentences (F(2,27) = 20.76, $P < 0.0001$).

DISCUSSION

We found that RHD patients with documented impairments in the perception of facial expression and prosody were also unable to discern the meaning of facial, prosodic, and gestural expressions of emotion when these displays were described using verbal language. This impairment is not reducible to an RH mediated defect in processing the specialized acoustic and visuospatial properties of nonverbal stimuli since the stimuli were presented verbally. This defect is also not reflective of RH specialization in the ability to interpret the emotional significance of events, as RHD patients performed comparably to LHD patients on Task 3 (Comprehension of Emotional Sentences). While the possibility remains that impaired performance on Task 2 (Verbal Descriptors of Nonverbal Expression) is due to the loss of ability to perform complex inferential processing, a capacity in which RHD patients are known to have deficits, we consider this explanation unlikely given that RHD patients displayed statistically comparable performance to LHD and NC on Level 3 interpretive sentences, those found to be the most difficult to interpret across diagnostic groups (*see* Table 5). Moreover, the sentences in Task 2 require a first grade reading level whereas the sentences in Task 3 require a fourth grade reading level.

These findings support two competing interpretations regarding the role of the RH in emotional communication. First, there may be two independent systems that are impaired following RHD: one system which is important in decoding the complex auditory and visual patterns present in nonverbal emotional expressions, and another which associates nonverbal behaviour with emotions. A second and more parsimonious hypothesis is that a hierarchical system mediates the comprehension of nonverbal communicative stimuli. Beginning with the most fundamental level for which hemisphere specialization occurs, previous research has documented RH predominance in the processing of visuospatial and acoustic stimuli. Our results replicate previous findings that the RH is involved in perceiving the communicative content of nonverbal expressions direct from facial (visuospatial) and prosodic (acoustic) stimuli. Moving up one level in the hierarchy, the RH may house category-specific lexical-semantic representations of nonverbal expressions, and RH lesions either destroy these representations or prevent them from being activated. The ability to comprehend the meaning of verbal descriptors of nonverbal expressions may also require the formation and interpretation of a mental image of these expressions, and RH damage may disrupt this ability (*see* Bowers *et al.*, 1990). The neural networks involved in the mediation of nonverbal communication do not extend their function to emotional interpretation in general, as the capacity to make culturally appropriate inferences regarding the emotional significance of events was preserved in RHD patients.

From a phylogenetic perspective, the finding that higher-order processors of nonverbal signals have evolved in the RH underscores the selective advantage that intonation and facial expression conferred during hominid evolution. While nonhuman primate communication appears in many ways homologous to human paralanguage, particularly in view of their shared subcortical representation (*see* Jürgens, 1979; Blonder *et al.*, 1989), our results confirm that nonverbal communication and its neural substructure continued to differentiate in association with the evolution of human language.

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REFERENCES

Benowitz LI, Bear DM, Rosenthal R, Mesulam MM, Zaidel E, Sperry RW (1983) Hemispheric specialization in nonverbal communication. *Cortex,* **19,** 5–11.

Blonder LX, Gur RE, Gur RC (1989) The effects of right and left hemiparkinsonism on prosody. *Brain and Language,* **36,** 193–207.

Borod JC, Caron HS (1980) Facedness and emotion related to lateral dominance, sex and expression type. *Neuropsychologia,* **18,** 237–241.

Bowers D, Bauer RM, Coslett HB, Heilman KM (1985) Processing of faces by patients with unilateral hemisphere lesions. *Brain and Cognition,* **4,** 258–272.

Bowers D, Coslett HB, Bauer RM, Speedie LJ, Heilman KM (1987) Comprehension of emotional prosody following unilateral hemispheric lesions: processing defect versus distraction defect. *Neuropsychologia,* **25,** 317–328.

Bowers D, Blonder L, Feinberg T, Heilman KM (1990) Emotional versus visual object imagery. *Journal of Clinical and Experimental Neuropsychology,* **12,** 84.

Brownell HH, Michel D, Powelson J, Gardner H (1983) Surprise but not coherence: sensitivity to verbal humor in right-hemisphere patients. *Brain and Language,* **18,** 20–27.

Bruyer R, Stroot C (1984) Lateral differences in face processing: task and modality effects. *Cortex,* **20,** 377–390.

Carmon A, Nachshon I (1973) Ear asymmetry in the perception of emotional non-verbal stimuli. *Acta Psychologica,* **37,** 351–357.

Cicchetti DV (1972) Extension of multiple-range tests to interaction tables in the analysis of variance: a rapid approximate solution. *Psychological Bulletin,* **77,** 405–408.

Cicone M, Wapner W, Gardner H (1980) Sensitivity to emotional expressions and situations in organic patients. *Cortex,* **16,** 145–158.

Damasio H, Damasio AR (1990) *Lesion Analysis in Neuropsychology.* New York: Oxford University Press.

DAVIDSON RJ (1984) Hemispheric asymmetry and emotion. In: *Approaches to Emotion*. Edited by K. R. Scherer and P. Ekman. Hillsdale, NJ: Lawrence Erlbaum, pp. 39–57.

DEKOSKY ST, HEILMAN KM, BOWERS D, VALENSTEIN E (1980) Recognition and discrimination of emotional faces and pictures. *Brain and Language*, **9**, 206–214.

ETCOFF NL (1984*a*) Perceptual and conceptual organization of facial emotions: hemispheric differences. *Brain and Cognition*, **3**, 385–412.

ETCOFF NL (1984*b*) Selective attention to facial identity and facial emotion. *Neuropsychologia*, **22**, 281–295.

FOLDI NS (1987) Appreciation of pragmatic interpretations of indirect commands: comparison of right and left hemisphere brain-damaged patients. *Brain and Language*, **31**, 88–108.

GARDNER H, DENES G (1973) Connotative judgements by aphasic patients on a pictorial adaptation of the semantic differential. *Cortex*, **9**, 183–196.

GARDNER H, LING PK, FLAMM L, SILVERMAN J (1975) Comprehension and appreciation of humorous material following brain damage. *Brain*, **98**, 399–412.

GARDNER H, BROWNELL HH, WAPNER W, MICHELOW D (1983) Missing the point: the role of the right hemisphere in the processing of complex linguistic materials. In: *Cognitive Processing in the Right Hemisphere*. Edited by E. Perecman. New York: Academic Press, pp. 169–191.

GRAVES R, LANDIS T, GOODGLASS H (1981) Laterality and sex differences for visual recognition of emotional and non-emotional words. *Neuropsychologia*, **19**, 95–102.

HEILMAN KM, SCHOLES R, WATSON RT (1975) Auditory affective agnosia: disturbed comprehension of affective speech. *Journal of Neurology, Neurosurgery and Psychiatry*, **38**, 69–72.

HEILMAN KM, BOWERS D, SPEEDIE L, COSLETT HB (1984) Comprehension of affective and nonaffective prosody. *Neurology, Cleveland*, **34**, 917–921.

JÜRGENS U (1979) Neural control of vocalization in nonhuman primates. In: *Neurobiology of Social Communication in Primates: An Evolutionary Perspective*. Edited by H. D. Steklis and M. J. Raleigh. New York and London: Academic Press, pp. 11–44.

LANDIS T, GRAVES R, GOODGLASS H (1982) Aphasic reading and writing: possible evidence for right hemisphere participation. *Cortex*, **18**, 105–112.

LEY RG (1980) *Emotion and the Right Hemisphere*. Doctoral dissertation. University of Waterloo.

LEY RG, BRYDEN MP (1979) Hemispheric differences in processing emotions and faces. *Brain and Language*, **7**, 127–138.

LEY R, BRYDEN M (1982) A dissociation of right and left hemisphere effects for recognizing emotional tone and verbal content. *Brain and Cognition*, **1**, 3–9.

LEY RG, BRYDEN MP (1983) Right hemisphere involvement in imagery and effect. In: *Cognitive Processing in the Right Hemisphere*. Edited by E. Perecman. New York: Academic Press, pp. 111–123.

MATSUI T, HIRANO A (1978) *An Atlas of the Human Brain for Computerized Tomography*. Tokyo: Igaku-Shoin.

MILNER B (1962) Laterality effects in audition. In: *Interhemispheric Relations and Cerebral Dominance*. Edited by V. B. Mountcastle. Baltimore: Johns Hopkins Press, pp. 177–195.

NATALE M, GUR RE, GUR RC (1983) Hemispheric asymmetries in processing emotional expressions. *Neuropsychologia*, **21**, 555–565.

ROSS ED (1981) The aprosodias: functional-anatomic organization of the affective components of language in the right hemisphere. *Archives of Neurology, Chicago*, **38**, 561–569.

ROSS ED, MESULAM M-M (1979) Dominant language functions of the right hemisphere? Prosody and emotional gesturing. *Archives of Neurology, Chicago*, **36**, 144–148.

SERGENT J, BINDRA D (1981) Differential hemispheric processing of faces: methodological considerations and reinterpretation. *Psychological Bulletin*, **89**, 541–554.

SIDTIS JJ (1980) On the nature of the cortical function underlying right hemisphere auditory perception. *Neuropsychologia*, **18**, 321–330.

SILBERMAN EK, WEINGARTNER H (1986) Hemispheric lateralization of functions related to emotion. *Brain and Cognition*, **5**, 322–353.

SUBERI M, MCKEEVER WF (1977) Differential right hemispheric memory storage of emotional and non-emotional faces. *Neuropsychologia*, **15**, 757–768.

TUCKER DM, WATSON RT, HEILMAN KM (1977) Discrimination and evocation of affectively intoned speech in patients with right parietal disease. *Neurology, Minneapolis*, **27**, 947–950.

WAPNER W, HAMBY S, GARDNER H (1981) The role of the right hemisphere in the apprehension of complex linguistic materials. *Brain and Language*, **14**, 15–33.

WECHSLER AF (1973) The effect of organic brain disease on recall of emotionally charged versus neutral narrative texts. *Neurology, Minneapolis*, **23**, 130–135.

WEINTRAUB S, MESULAM M-M, KRAMER L (1981) Disturbances in prosody: a right-hemisphere contribution to language. *Archives of Neurology, Chicago*, **38**, 742–744.

WINNER E, GARDNER H (1977) The comprehension of metaphor in brain-damaged patients. *Brian*, **100**, 717–729

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RECOGNITION OF MOTION-DEFINED SHAPES IN PATIENTS WITH MULTIPLE SCLEROSIS AND OPTIC NEURITIS

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SUMMARY

We have developed a simple procedure for assessing the ability of the visual pathway to extract a two-dimensional shape from motion. The test requires a patient to read motion-defined (MD) letters. These letters differ physically from the familiar contrast-defined (CD) letters that are dimmer or brighter than their surroundings in that the boundaries of MD letters are rendered visible exclusively by a step in velocity while the boundaries of CD letters are rendered visible by a step in luminance.

Subjects viewed a random pattern of bright dots containing a perfectly camouflaged letter. Then the letter was revealed by moving dots within and outside the letter at equal speeds in opposite directions. Letter reading scores for 50 eyes of 25 patients with multiple sclerosis (MS) or optic neuritis were compared with norms based on 50 control subjects. When tested with large (50 arc min, i.e., 6/60) MD letters, 34/50 eyes of patients required abnormally high dot speeds to read letters, visual loss being sufficiently selective in 10 eyes that contrast sensitivity, Snellen acuity, 11%-contrast and 4%-contrast acuity were all spared. Four eyes were effectively motion blind in the sense that they could not read large letters even at our highest relative speed of 0.9 deg/s and the failure could not be attributed to reduced Snellen acuity. Our normal limit was 2.5 SD from the control mean and there were 1/50 false positives. Of the 34/50 eyes with elevated speed thresholds, 23 had normal Snellen acuities. The number of eyes abnormal for intermediate (11%) contrast CD letters, was 19/50 of which 8 had normal Snellen acuity, confirming our previous finding that MS can degrade the ability to see low-contrast objects while sparing Snellen acuity.

We conclude that MD test letters can detect lesions that are not picked up by testing with CD test letters of high or low contrast. We suggest that the MD letter test can detect dysfunction in the human equivalent of a pathway in monkey brain that originates in large retinal ganglion cells, passes through the magnocellular layers of the lateral geniculate body, includes cortical area MT, and is involved in processing motion.

INTRODUCTION

It is not many years since the functional map of human visual cortex given in textbooks amounted to little more than a single point-to-point retinotopic map in Brodmann's area 17 (i.e., striate cortex) surrounded by a region labelled the 'visuopsychic area' or 'association cortex' that included Brodmann's areas 18 and 19, and in reality was a functional terra incognita (Brodmann, 1908, 1914; Johnston and Whillis, 1954; Braak, 1980). Thirty-five years ago, techniques for investigating the functional organization of the intact human brain were severely limited, and even in the nonhuman primate the functional mapping of visual cortex was still restricted to recording local evoked potentials (Talbot and Marshall, 1941). Much of our knowledge of visual cortical mapping

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in man was inferred from the sensory consequences of focal brain lesions sustained during the Russo-Japanese War of 1904–1905 and the 1914–1918, 1939–1945 and Korean conflicts (Holmes, 1919; Spalding, 1952; Teuber *et al.*, 1960; Glickstein and Whitteridge, 1987), but such maps are of low spatial resolution, and inferences about normal function based on the sensory effects of lesions are subject to well-known caveats (Glassman, 1978). There are several accounts of visual sensations produced by local stimulation of the brain either during surgery (Penfield and Rasmussen, 1950; Penfield and Jasper, 1954) or, in more recent years, after implantation of electrodes (Brindley and Lewin, 1968), but such reports are few and fragmentary. During the last 30 yrs several methods have been developed for investigating visual processing in the intact human brain including techniques for recording electrical and magnetic brain responses evoked by visual stimulation (reviewed in Regan, 1972, 1989*a*), positron emission tomography (PET) and regional cerebral blood flow studies (Sokoloff, 1985), but the demarcation and location of multiple visual projections in man remains far cruder than the mapping precision that has been attained in nonhuman primates. Consequently, a great deal of our current understanding of the detailed organization of the human visual cortex is extrapolated from the results of physiological studies on the nonhuman primate (Daniel and Whitteridge, 1961; Zeki, 1969, 1971; Woolsey, 1971; Hubel and Wiesel, 1977; Livingstone and Hubel, 1984, 1987; Van Essen, 1985; Merigan and Eskin, 1986; Schiller, 1986; Maunsell and Newsome, 1987; De Yoe and Van Essen, 1988).

Studies on the visual pathway of the macaque monkey have revealed two major pathways (or 'streams') that are already distinct at retinal level. One (the M stream) passes through the magnocellular layers of the lateral geniculate nucleus (LGN), and the other (the P stream) passes through the parvocellular layers of the LGN. The distinction between the M and P streams is preserved up to the layers of entry in the striate cortex, and in some degree far into the prestriate cortex (Maunsell and Newsome, 1987; De Yoe and Van Essen, 1988). At least 11 separate retinotopic projections have been documented in primate visual cortex in addition to the many retinotopic projections in subcortical nuclei and the 9 or more other cortical areas that receive visual inputs that are poorly or not at all retinotopic (Zeki, 1969, 1971, 1973, 1974, 1980; Allman and Kaas, 1971, 1974*a*, *b*, 1975, 1976; Tigges and Tigges, 1985; Van Essen, 1985). The visual cortical areas with relatively ordered projections include V1, V2, V3, V4 and MT (also called V5). Fig. 1 illustrates the neuroanatomical locations of several visual areas in the cortex of Macaca mulatta (i.e., the old-world Rhesus monkey). For our present purpose, the crucial point is that, according to the microelectrode evidence, different cortical areas have different functional properties, although this is not to suggest that any particular visual dimension such as, for example, motion, colour or spatial form is entirely mediated by one visual area. Nevertheless, it has been proposed that the perception of movement is mediated by a predominantly M stream achromatic pathway that includes area MT (Van Essen *et al.*, 1981; Ungerleider and Mishkin, 1982; Maunsell and Van Essen, 1983; Zihl *et al.*, 1983; Zeki, 1974; Allman *et al.*, 1985; Movshon *et al.*, 1985; Shipp and Zeki, 1985; Van Essen, 1985), while the perception of colour and form is mediated by a predominantly P stream pathway that includes area V4 (Zeki, 1973, 1983; Pearlman *et al.*, 1979; Damasio *et al.*, 1980; Desimone *et al.*, 1985; Desimone and Ungerleider, 1986). This hypothesis is illustrated in fig. 2.

In man, there is evoked potential evidence for two parallel pathways that are separate

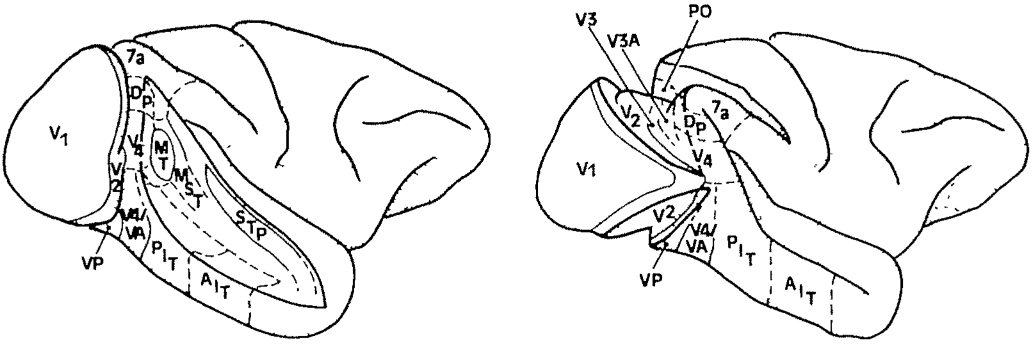

FIG. 1. Location of visual areas in macaque monkey cortex. The *left half* of the figure is a lateral view in which the superior temporal sulcus has been opened to show the positions of visual areas within it. Visual areas that are normally hidden within the sulcus include middle temporal (MT), the medial superior temporal (MST) and the superior temporal polysensory area (STP). In the *right half* of the figure the lunate, intraparietal and inferior occipital sulci have been opened to expose parts of the visual areas V3, V3A and the ventral posterior area (VP) A portion of the parieto-occipital area (PO) can be seen in the medial wall of the intraparietal sulcus. Abbreviations for visual areas: AIT = anterior inferotemporal; DP = dorsal prelunate, PIT = posterior inferotemporal; VA = ventral anterior. From J. H Maunsell and W T. Newsome (1987), reprinted with permission.

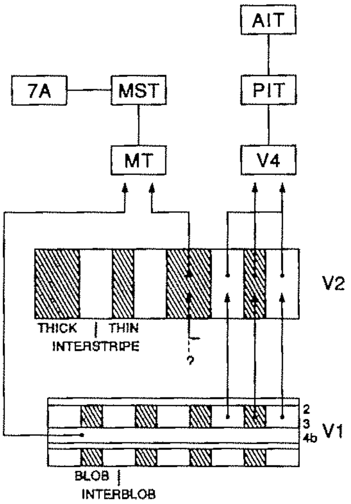

FIG. 2 Major components of the motion pathway and the colour and form pathway in macaque monkey. Segregation of the two pathways is evident in cortical area V1, where the colour and form pathway arises from the blobs and interblob regions in layers 2 and 3. These regions project to the thin stripes and interstripes in cortical area V2, which in turn project to cortical area V4. The outputs of V4 lead to cortical areas PIT and AIT. The motion pathway is found in layer 4b in V1, which projects directly to cortical area MT MT also receives a projection from the thick stripes in V2, whose inputs are not yet established The outputs of MT lead to more central cortical areas including MST and area 7a. From Maunsell and Newsome (1987), reprinted with permission.

from peripheral level, one colour-coded and strongly driven by flicker at about 16 Hz, and the other achromatic and strongly driven by flicker at about 40 Hz (Regan, 1968*a*, *b*, 1970, 1989*a*; van der Tweel and Spekreijse, 1969).

Behavioural evidence that monkey area MT is important in processing motion information has been obtained by demonstrating that small chemical lesions in MT produce defects in psychophysical responses to motion (Newsome *et al.*, 1985*a*, *b*; Lisberger *et al.*, 1987) and that electrical stimulation of local regions within MT can systematically bias psychophysical responses to motion to favour one direction or the opposite direction (Saltzman *et al.*, 1990). In the human, a small lateral region of Brodmann area 19 shares distinctive myeloarchitectonic features with macaque monkey MT (Sereno *et al.*, 1988), and clinical observations indicate that lesions involving this cortical area in the human can affect the visual perception of position or movement without affecting the ability to recognize objects (Ratcliff and Davies-Jones, 1972; Damasio and Benton, 1979). A relevant study in a human who showed degraded motion perception after experiencing cortical damage was reported by Zihl *et al.* (1983). This takes us to the question of how emerging knowledge of the functional architecture of monkey brain might be used to guide studies on human patients.

While neurophysiologists have been engaged in an attempt to associate different neural structures with different functions—typically by means of techniques that would be unethical in human—there is a history of at least a hundred years of endeavour using noninvasive psychophysical methods to achieve what can be regarded as a kind of 'functional dissection' of the human visual pathway. This endeavour has produced a body of psychophysical evidence that visual sensitivities to colour, luminance, contrast, orientation, spatial frequency, position-in-depth, motion-in-depth and sideways motion are substantially (though not completely) independent. A suggested explanation is that, functionally, the human visual pathway can be regarded as an array of parallel processors or 'sets of channels', each sensitive to a different submodality (reviewed in Regan, 1982).

The psychophysical channelling hypothesis can be used to advance our knowledge of the mechanisms of disorders that affect visual pathway function by providing a means of applying knowledge obtained in animal research to study human disease mechanisms. Our argument is that visual sensitivities that are more or less independent of one another reflect separate and physically-distinct neural processing, so that these specific sensitivities may be damaged differentially by disease (Regan, 1979, 1982, 1990, 1991). At least so far as cerebral damage is concerned, this concept stands in sharp contrast with the view of Teuber (1960) who considered that the visual consequences of such damage reflects the different vulnerabilities of visual functions rather than selective impairments.

A rationale for exploiting psychophysical channelling ideas to elucidate the mechanism of a neuro-ophthalmological disorder is as follows: (1) by using psychophysical methods test a patient's visual sensitivities to the different visual submodalities listed above, in order to identify the set or sets of channels that are affected by the disorder; (2) by putting this information together with our emerging knowledge of the monkey visual pathway, infer the cortical visual area(s) or classes of neurons that, in human patients, are affected by the disorder. The properties of the affected neurons can then be compared with the properties of those that are spared, with the aim of identifying physiological reasons for the selective vulnerability of the affected neurons.

This rationale has guided previous studies of contrast sensitivity to sinewave gratings in patients with multiple sclerosis (MS) and optic neuritis (ON). Some patients experienced sensitivity loss for gratings of high spatial frequency (and, therefore, showed reduced Snellen acuity), while sensitivity to low spatial frequencies was relatively spared. Other patients showed the opposite pattern of loss: sensitivity to low spatial frequency was lost while Snellen acuity was spared. A third class of patient showed selective loss for a broad range of intermediate spatial frequencies, while a fourth class experienced unselective sensitivity loss for all spatial frequencies (Regan *et al.*, 1977; Bodis-Wollner *et al.*, 1979; Zimmern *et al.*, 1979). We suggested that MS or ON can differentially affect the higher, intermediate and low spatial frequency channels and that visual acuity tests such as the Snellen test are inadequate, because acuity tests assess sensitivity to high spatial frequencies only, and do not assess sensitivity to low spatial frequencies (Regan *et al.*, 1977). These patterns of visual loss may correspond to the finding that the primate visual pathway contains neurons that respond most strongly to low spatial frequencies while others respond best to high spatial frequencies (De Valois *et al.*, 1982). In particular, the patterns of contrast sensitivity loss in MS and ON can be understood if these disorders differentially damage neurons that respond best to low, intermediate and high spatial frequencies (Regan *et al.*, 1977). On the grounds that M cells have generally higher contrast sensitivity than P cells to temporally-modulated gratings (Shapley *et al.*, 1981), we further suggested that the selective loss of sensitivity shown by some patients for 8 Hz counterphase-modulated gratings of low contrast and low spatial frequency reflects selective damage to (probably Y-type) M-stream neurons (Regan and Maxner, 1986).

Although the present study shares the same psychophysical channelling rationale as the contrast sensitivity studies just described it has quite a different focus. Our finding that MS can elevate motion/flicker threshold for gratings of low spatial frequencies that were counterphase-modulated at 8 Hz while sparing visual acuity suggests that the disease can selectively affect neurons that carry motion information (Holliday and Ruddock, 1983; Regan and Maxner, 1986). We therefore designed a simple procedure for testing the ability to process motion (Regan and Hong, 1990). The test resembles a conventional letter reading test except that neurons sensitive to relative motion are required to see the letters at all. But our procedure tests more than sensitivity to relative motion. Neurons for discriminating the shapes of two-dimensional motion-derived form are also required for accurate letter recognition.

METHODS

Test stimuli and test procedures

1. *Motion-defined (MD) dotted letters.* A random pattern of bright dots of near 100% contrast was generated on a CRT monitor by an IBM AT personal computer with an ATI Wonder EGA graphics card. There were 320 (horizontal)×200 pixels. Each dot occupied 4×4 pixels, so that there were 80×50 dots in all. Viewing was from 6 m, at which distance the pattern subtended 2.3° (horizontal)×1.5°. At this distance each dot subtended 2.3 arc min. The dot pattern contained a camouflaged letter that could not be detected when the dots were stationary or moving as a whole. Fig. 3A illustrates the effectiveness with which the letter was camouflaged when all dots were stationary. The letter was made visible by moving the dots within the letter rightwards at V deg/s while moving the dots outside the letter leftwards at V deg/s, so that relative velocity was 2V deg/s. The dots were switched on the instant that they started moving. Note that the letter itself was stationary. The onset of each 4 s letter presentation was signalled by a tone. After each letter presentation the dots were switched off. Fig. 3B illustrates that, although the letter was clearly visible to the eye, the camera could not detect the letter. In a control experiment eye movements were monitored using a Stanford Research Institute double-Purkinje eye tracker, and it was confirmed that a centrally-viewed moving dot stimulus of small angular subtense (2.3°×1.5°) did not evoke eye movements.

For each letter size there were 10 letters. There were 6 letter sizes, each successive width differing by the same proportion of $1{:}(2)^{1/2}$ (i.e., 1:1.4), so that letter sizes were equally spaced on a logarithmic scale. The width of each stroke in the letter was approximately one-fifth of the letter width. These letter sizes were equivalent to Snellen lines ranging from 6/60 (i.e., 0.10 decimal acuity) to 6/10.8 (i.e., 0.55 decimal acuity). The largest and smallest letters subtended 50.0 and 9.1 arc min respectively, at 6 m viewing distance.

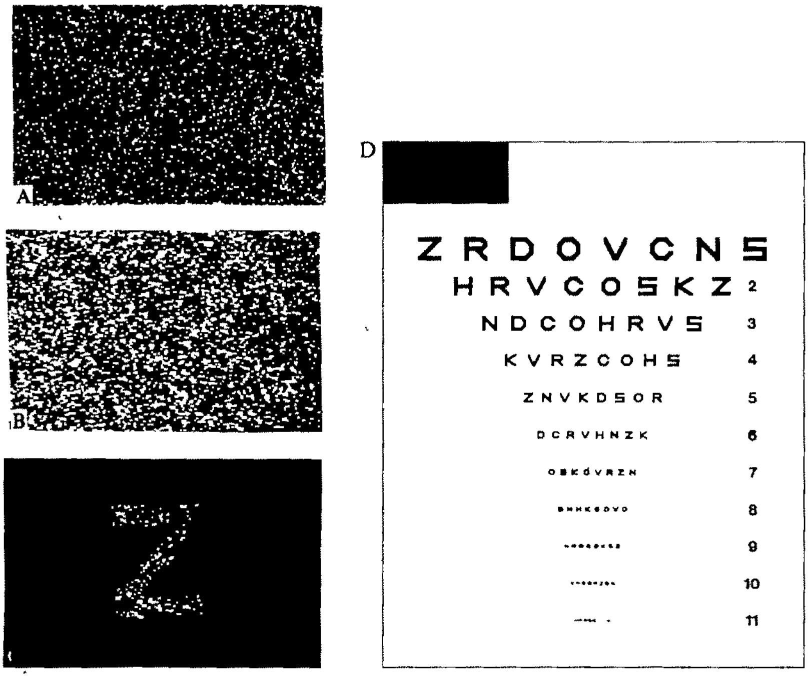

FIG. 3. A, stationary random dot pattern containing a perfectly camouflaged letter. B, dots within a Z-shaped area at the centre of the screen moved rightwards while dots outside the letter moved leftwards at the same speed. The letter was clearly visible to the eye, because its boundaries were defined by a sharp difference of velocity, i.e., by velocity contrast. However, this photographic time exposure did not reveal the letter because the camera did not distinguish between opposite directions of dot motion. C, the letter in B was revealed to the camera by switching off all dots outside the letter. This letter is clearly visible because its boundaries are defined by sharp step in luminance, i.e., by luminance contrast. D, Snellen-type line chart used in this study.

The test procedure was as follows. To measure motion sensitivity, all 10 letters were presented in random order at the highest dot speed of 0.45 deg/s, all with the same letter size of 50 arc min subtense. Subjects were instructed to state which letter had been presented and, if uncertain, to guess. Presentation duration was 4 s and subjects were allowed 3 s to respond. Then all 10 letters were presented at the next fastest dot speed and so on. Seven dot speeds were available in steps of 2:1. Speed threshold for MD dotted letters was defined as the dot speed in deg/s for 75% correct reading score obtained by plotting the percentage of correct responses versus dot speed. Motion sensitivity for MD dotted letters, defined as the reciprocal of speed threshold, was plotted as ordinate in figs 4–9.

Visual acuity for MD dotted letters was measured with dot speed held at a constant 0.45 deg/s throughout the measurement. First, all the largest 10 letters were presented, then all the 10 next largest and so on. Visual acuity, defined as the letter size for 75% reading accuracy was calculated by plotting the percentage of correct responses versus letter size.

2. *Contrast-defined dotted letters.* Uncamouflaged contrast-defined (CD) dotted letters were presented in exactly the same way as MD letters except that all dots outside the letter were switched off so that letters appeared as an array of bright dots, on a homogeneous dimmer background (*see* fig. 3c). Dot speed was always 0.45 deg/s.

In order to vary dot contrast, the CRT monitor was optically superimposed on a uniform background light subtending 4.0° (horizontal)×3.6°. For calibration purposes the field of view could be divided into two by a vertical boundary, the left side being illuminated by the monitor so as to present a homogeneous area that had the same luminance as the bright dots. The right side of the field was illuminated by the background light alone. In order to match the luminance of the two halves of the field a neutral density filter was placed in front of the CRT monitor and a second filter was placed in front of the uniform background field. When varying dot contrast, the two filters were altered together so as to keep mean luminance constant at 80 cd/m^2. Precision was better than 0.1 log unit.

Dot contrast (C%) was defined as 100 (L_D/L_B) where L_D was the luminance of a dot in the absence of the background light and L_B was the luminance of the superimposed background light. Contrast threshold was measured by presenting all 10 letters at the highest dot contrast, then at a contrast 0.1 log units lower, then at a further 0.1 log units lower contrast, and so on. Letter size was held constant throughout this measurement at 50 arc min. Contrast threshold (as a percentage) for 75% correct reading accuracy was calculated by plotting the percentage of correct responses versus dot contrast (C%) Contrast sensitivity, defined as the reciprocal of contrast threshold, was plotted as abscissa in fig. 4.

3. *Contrast-defined (CD) solid letters.* Snellen line acuity was measured using the chart illustrated in fig. 3D in which letter sizes were equally spaced on a logarithmic scale, though spacing was somewhat finer than for the dotted letters at 1:$(2)^{1/3}$ (i.e., 1:1.26). Isolated-letter acuities were measured using square white cards that measured 14.5×14.5 cm. Each card had a dark letter at the centre. Letter sizes were the same as for the fig. 3D chart, and there were 10 cards, each with a different letter, for each letter size. There was one set of cards with 96% contrast, one with 11% contrast and one with letters of 4% contrast. Isolated-letter cards were presented through a square hole of 2.4° side length in a matt white screen subtending 14° (horizontal)×19°. The front of the screen was illuminated by tungsten light to a luminance of 100 cd/m^2 in order to maintain the eye at a constant level of light adaptation. The Snellen chart was hung on the front of the screen. Visual acuities (for 75% correct reading scores) were calculated by plotting the percentage of correct responses versus letter size.

Calculation of interocular differences

In tests 1–3 above, all control data were based on 50 eyes of 50 control subjects, 1 eye per subject. Interocular control data were based on 100 eyes of these 50 control subjects. In any given individual, let the visual acuity for dotted MD letters be VAM_L for the left eye and VAM_R for the right eye. Visual acuities for the two eyes were compared by calculating the ratio of the decimal VAs for left and right eyes with the larger visual acuity as numerator, so that interocular ratios were always greater than unity. The mean and SD for these individual interocular ratios was calculated for the control group (50 pairs of eyes), and the upper normal limit set equal to 2.5 SDs from the control group mean. The interocular ratio of speed thresholds for large dotted MD letters was calculated as $(STM_L)/(STM_R)$ or $(STM_R)/(STM_L)$, whichever was greater than unity, where STM_L and STM_R were speed thresholds for left and right eyes, respectively. The upper normal limit for interocular ratio was calculated as described above for visual acuity.

The recommended method for using low-contrast acuity charts to test vision in patients is to normalize low-contrast acuity with respect to high-contrast (i.e., Snellen) acuity in individual patients, rather than using low-contrast acuity alone (Regan, 1989*c*). This was done by calculating the ratio between decimal visual acuity for the high-contrast chart and visual acuity for the 4% or 11% contrast chart. Thus

$$(VAC_N)_{11} = (VAC_{96})/(VAC_{11}), \quad \text{and}$$
$$(VAC_N)_4 = (VAC_{96})/(VAC_4),$$

where VAC was the visual acuity for the 96%, 11% or 4% chart, VAC_N was normalized acuity, and the subscript numbers indicated letter contrast. For letters of 11% contrast we compared normalized acuities for left and right eyes by calculating, for each individual subject, the ratio between the values of $(VAC_N)_{11}$ for the left and right eyes with the larger $(VAC_N)_{11}$ as numerator to ensure that all ratios were positive. A similar calculation was made for letters of 4% contrast. The reason for this approach was to allow for the experimental finding that control subjects with good Snellen acuity also tend to have good low-contrast acuity. Thus a given value of low-contrast acuity can be within normal limits in a patient with 6/6 Snellen acuity, although in a second patient with 6/3 Snellen acuity this same value of low-contrast acuity would be abnormally low (Regan and Neima, 1983; Regan, 1988*a*).

Refraction and ocular assessment at test time

The vision of control subjects and patients was assessed by one of us (A.C.K., an optometrist) immediately before testing. Each eye was refracted, and Snellen acuity was measured at 6 m and at 0.4 m. Binocularity

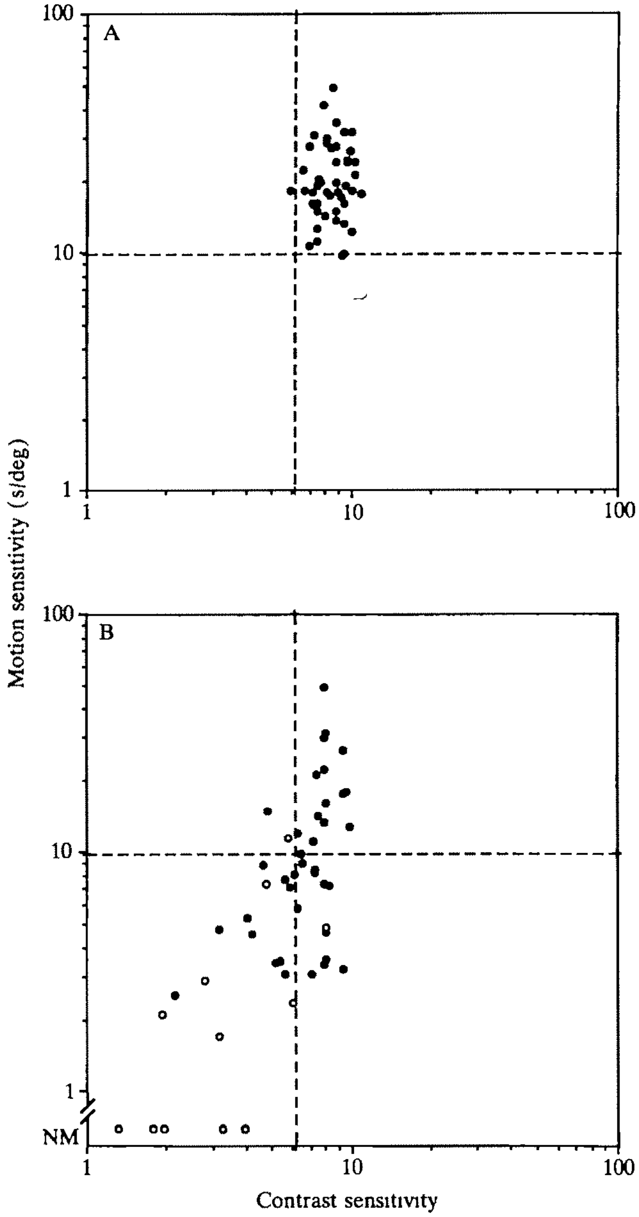

FIG. 4 Motion sensitivity for large motion-defined dotted letters versus contrast sensitivity for large contrast-defined dotted letters. Ordinates plot the reciprocal of the speed that gave 75% reading scores for dotted motion-defined letters of fixed size (50 arc min subtense, i e , 6/60 Snellen equivalent). Abscissae plot the reciprocal of the luminance contrast that gave 75% reading scores for uncamouflaged dotted letters of the same size (fig. 3c) A, data for 50 eyes of 50 control subjects. B, data for 50 eyes of 25 patients. Open circles = eyes with low Snellen acuities (>2.5 SD below the control group mean). Closed circles = normal Snellen acuity. Eyes marked NM (not measurable) gave reading scores for motion-defined letters that were so poor that motion sensitivity could not be measured.

was checked by means of the cover test at 6 m and at 0.4 m. Stereoacuity was measured at 0.4 m using the Randot test.

Patients and control subjects

All tests were conducted on two groups of subjects—50 controls and 25 patients with MS or ON. The control group comprised 10 males and 40 females and was age and sex-matched with the patient group. The age range was 24–56 yrs and mean age 39 (SD = 9) yrs. The 25 patients included 3 males and 22 females. Their age range was 21–52 yrs, and mean age 38 (SD = 9) yrs. The diagnostic criteria for MS were those set out by Schumacher *et al.* (1965) according to the scheme described by Rose *et al.* (1976). Appendix 1 sets out the clinical data for all patients.

RESULTS

Motion sensitivity for large dotted motion-defined (MD) letters versus contrast sensitivity for large dotted contrast-defined (CD) letters

Although this experiment resembled the experiments of figs 6–9 in that we compared reading scores for dotted MD letters with reading scores for uncamouflaged CD letters, this first experiment had the special feature that the two kinds of letters were identical in all respects except one. In particular, the spatial sampling (i.e., dottiness) of the two kinds of letter were identical. For this reason, CD letter stimuli were created by switching off all dots surrounding the letter. In this first experiment the MD and uncamouflaged letters were always the same unvarying size (Sections 1 and 2 in Methods).

In this, as in all the experiments described below, subjects reported informally that the dotted MD letters were invisible when dot speed was zero, and we went on to confirm formally a previous report that letter reading scores did not differ from chance at zero dot speed (Regan and Hong, 1990). When the dots inside the letter and outside the letter moved in opposite directions at very low speed, subjects reported that the letters could just be seen (i.e., letters were just segregated from their surroundings), but they appeared fuzzy and subjects made many reading errors even for the fixed large 6/60 letter size used in this experiment. As the dot speed was progressively increased the letters appeared sharper, and subjects made fewer and fewer reading errors. Motion sensitivity, plotted as ordinate in fig. 4, was defined as the reciprocal of the dot speed that gave 75% reading accuracy. Contrast sensitivity for CD dotted letters, defined as the reciprocal of the contrast that gave 75% reading accuracy, is plotted as abscissa in fig. 4. (A CD dotted letter is illustrated in fig. 3c.)

For the reader's convenience, fig. 4 shows the lower normal limits for speed sensitivity (horizontal dashed line) and contrast sensitivity (vertical dashed line). These limits were set at 2.5 SDs from the respective means for the control group so that, on average, only 1 in 100 of the control group would be rated incorrectly as abnormal (i.e., the expected false-positive rate would be 1 in 100).

Fig. 4A shows that data points for 50 eyes of 50 control subjects were tightly grouped for both motion and contrast sensitivities. In this control group the false-positive rate was 1/50 for both measures. To informal visual inspection fig. 4A gave no impression that, in control subjects, motion sensitivity for large MD dotted letters was systematically related to contrast sensitivity for large uncamouflaged dotted letters. This impression was confirmed when the correlation coefficient was calculated to be 0.05 ($P = 0.72$).

Results for 50 eyes of 25 patients, shown in fig. 4B, presented a quite different picture to the control data of fig. 4A. Taking the patient group as a whole, there was a tendency for motion sensitivity to correlate with contrast sensitivity (correlation coefficient 0.71, $P = 0.0001$), although—and this is the crucial finding here—some individual eyes showed a marked dissociation between motion sensitivity and contrast sensitivity.

Fig. 4B and Appendix 2 show that 34/50 eyes fell below the horizontal dashed line, i.e., these eyes had abnormally low motion sensitivity for dotted motion-defined letters, and 22/50 eyes fell to the left of the vertical dotted line, i.e., these eyes had abnormally low contrast sensitivity for uncamouflaged CD dotted letters. Of 36 eyes that were abnormal in one or other test, 14 (13 of which had normal Snellen acuity) were abnormal for MD letters, but had normal contrast sensitivity for dotted CD letters. Because the letters used in this experiment were identical in dottiness and size, this finding indicates that the neural mechanisms that process MD letters and CD letters are sufficiently different that they can be differentially damaged by demyelinating disease. Two eyes were abnormal for CD letters, but not for MD letters and, of these 2 eyes, 1 had normal Snellen acuity. Motion and contrast sensitivities were both abnormal in 20 eyes and, of these 20 eyes, 10 had normal Snellen acuity.

Five eyes marked NM (not measurable) below the break in the ordinate in fig. 4 scored at chance level at the fastest dot speed we could produce (0.45 deg/s dot speed, that is, a relative dot speed between letter and surround of 0.90 deg/s). Insensitivity to MD letters could not be attributed to reduced Snellen acuity in 4 of these 5 eyes, all of which had decimal visual acuity better than 0.5, because control experiments showed that motion sensitivity for MD letters remained within normal limits when the visual acuity of a control eye with acuity of 1.0 or better was reduced to 0.5 by placing a positive lens before the eye so as to blur the retinal image. In order to reduce the reading score at the fastest dot speed from 100% correct to 50% correct, a blurring lens of approximately +3.0 dioptres was required that reduced decimal visual acuity from 1.0 or better to approximately 0.25.

Motion sensitivity for large motion-defined letters versus visual acuity for small motion-defined letters

Our rationale for this second experiment was by way of analogy with the finding that some patients with MS or ON who have normal contrast sensitivity for fine, high-contrast detail have low sensitivity for coarse, low-contrast detail (Regan *et al.*, 1977; Bodis-Wollner *et al.*, 1979; Zimmern *et al.*, 1979; Regan and Maxner, 1986). If we suppose that relative dot speed is analogous to contrast in that the visibility of an MD letter is determined by relative dot speed while the visibility of a CD letter is determined by contrast, we might envisage that some patients with normal visual acuity for small MD letters of high dot speed would have low motion sensitivity for large MD letters of low dot speed. Therefore, in this experiment we compared reading scores for large MD letters of low dot speed with reading scores for small MD letters of high dot speed (Section 1 in Methods). Fig. 5 plots motion sensitivity for 6/60 dotted MD letters versus visual acuity for MD letters of fixed 0.45 deg/s dot speed.

Fig. 5A shows that data points for 50 eyes of 50 control subjects were tightly grouped for both motion sensitivity and acuity. With our 2.5 SD upper normal limits there were 1/50 false positives for both measures. Fig. 5B shows that 34/50 eyes fell below the horizontal dashed line (i.e., had slow motion sensitivity for large letters of low velocity contrast), of which 23/34 eyes had normal Snellen acuity (filled circles). Fig. 5B also shows that 19/50 eyes had subnormal acuity for motion-defined dotted letters, of which 10/19 eyes had normal Snellen acuity. Of the 34 eyes with abnormally low motion

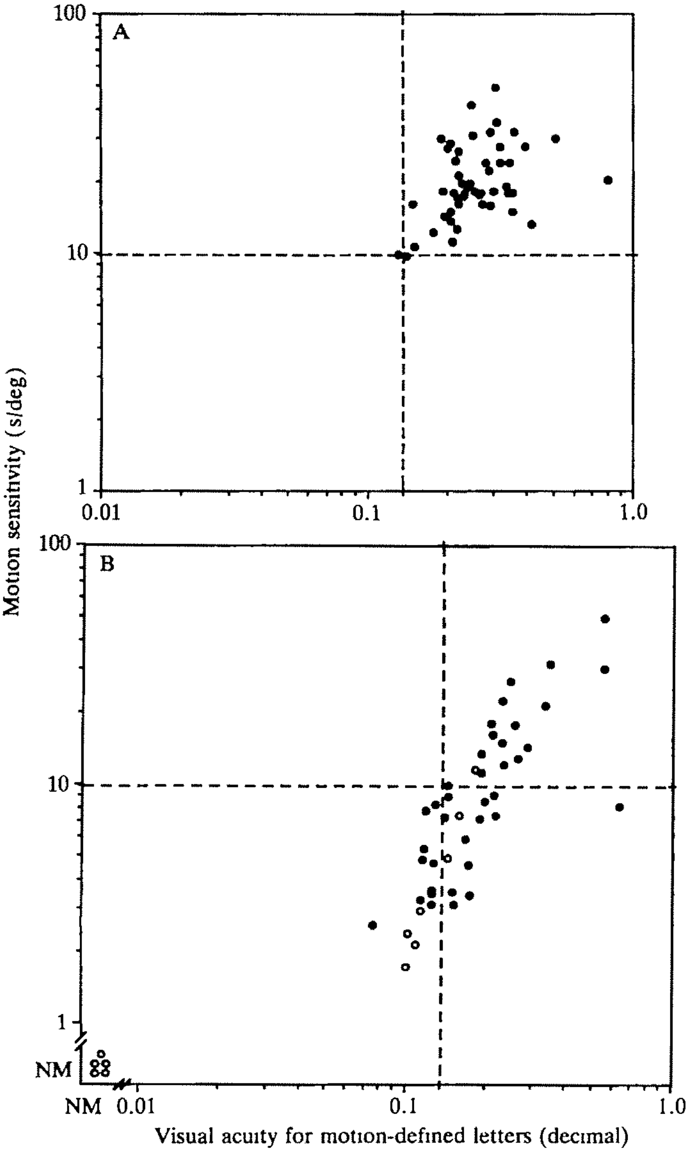

FIG. 5. Sensitivity to large motion-defined dotted letters versus visual acuity for small motion-defined dotted letters. Ordinates plot the reciprocal of the speed that gave 75% correct reading scores for dotted motion-defined letters of fixed large size (50 arc min subtense, i.e., 6/60 Snellen equivalent). Abscissae plot visual acuity for motion-defined letters of high dot speed held constant at 0.45 deg/s (i.e., the speed difference between dots inside and outside the letter was 0.9 deg/s). A, data for 50 eyes of 50 control subjects. B, data for 50 eyes of 25 patients. Open circles = eyes with low Snellen acuities (>2.5 SD below the control group mean). Closed circles = normal Snellen acuity. NM = not measurable.

sensitivity for large motion-defined letters, visual acuity for motion-defined letters was within normal limits for 15, of whom only 13/15 had normal Snellen acuity. No eye showed the converse pattern of loss, i.e., low visual acuity for motion-defined dotted letters accompanied by normal motion sensitivity for large motion-defined dotted letters.

Motion sensitivity for large motion-defined letters versus visual acuity for solid letters

The test letters that have been used in published studies of high and low-contrast acuity in patients wth MS and other disorders were solid rather than being dotted as in our first two experiments described above (Regan and Neima, 1983; Moskowitz *et al.*, 1985; Lerner *et al.*, 1986; Regan and Maxner, 1986, 1987; Drucker *et al.*, 1988; France and France, 1988; Kleiner *et al.*, 1988; Regan, 1988*a*, *b*; Sturr *et al.*, 1989). With the aim of comparing our data for MD letters more closely with previous findings we therefore used solid CD letters (Section 3, Methods) rather than the dotted CD letters (Section 2, Methods) used in our second experiment. The purpose of this third experiment was to find whether the MD letter test detected abnormality that was hidden to high, intermediate and low-contrast solid CD letters.

Rather than using a line (Snellen) format for the solid letters we first used the isolated-letter format illustrated in fig. 3E, F. Our reasoning here was that the 'crowding' or lateral interaction effect can influence reading performance when acuity is measured with a Snellen chart (Flom *et al.*, 1963; Schapero, 1971), and intersubject variations in crowding might have introduced spurious noise into our comparison of visual acuities for motion-defined and contrast-defined letters. Finally we measured Snellen line acuity using the chart illustrated in fig. 3D.

Isolated letters of high, intermediate and low contrasts: monocular data

Fig. 6 shows data for high-contrast isolated letters. Correlation coefficients in fig. 6A and B were, respectively, 0.32 ($P = 0.025$) and 0.66 ($P = 0.0001$), indicating that, in controls as well as patients, there was an overall tendency for sensitivity to MD letters to be degraded in eyes with low acuity for CD letters. But again, as in the experiments reported above, the two measures were quite dissociated in some eyes of the patient group. Our main finding here was that 24 of the 34 eyes that had low motion sensitivity for large MD dotted letters had normal acuity for isolated, solid, 96%-contrast CD letters and, of these 24 eyes, 22 also had normal Snellen acuity (filled circles). Conversely, none of the 10/50 eyes with low acuity for isolated, solid, 96%-contrast CD letters had normal motion sensitivity for large MD dotted letters. In 10 eyes the two measures were both abnormal, and Snellen acuity was normal in only 1 of these 10 eyes.

Fig. 7 shows data for 11%-contrast solid letters. Correlation coefficients in fig. 7A and B were, respectively, 0.27 ($P = 0.06$) and 0.64 ($P = 0.0001$), indicating that, in patients, there was an overall tendency for sensitivity to MD letters to be low in eyes with low acuity for CD letters. But again, as in the experiments reported above, the two measures were quite dissociated in some eyes of the patient group. Our main finding was that 16 of the 34 eyes that had low motion sensitivity for large MD dotted letters had normal acuity for isolated, solid, 11%-contrast CD letters and that all of these 16 eyes also had normal Snellen acuity (filled circles). Conversely, only one of the 19/50 eyes with low acuity for isolated, solid, 11%-contrast CD letters had normal motion

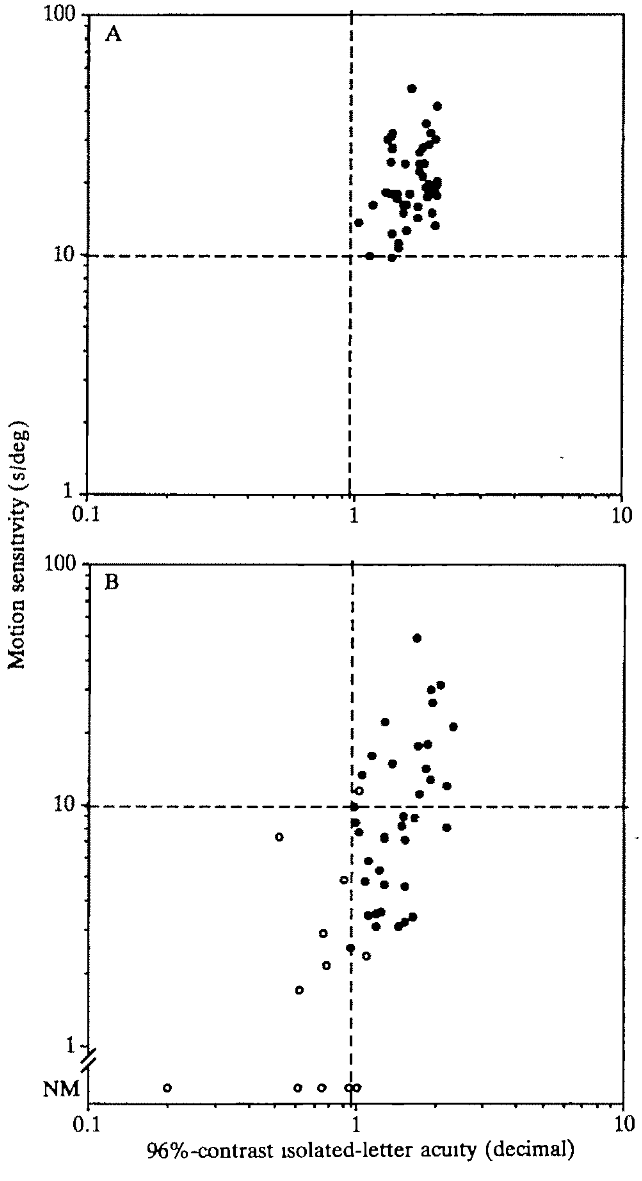

FIG. 6. Sensitivity to large motion-defined dotted letters versus visual acuity for isolated solid contrast-defined letters of 96%-contrast Ordinates plot the reciprocal of the dot speed that gave 75% reading scores for dotted motion-defined letters of fixed size (50 arc min subtense, i e , 6/60 Snellen equivalent). Open circles = eyes with low Snellen acuities (>2.5 SD below the control group mean). Closed circles = normal Snellen acuity A, controls; B, patients

sensitivity for large MD dotted letters. In 18 eyes the two measures were both abnormal, and Snellen acuity was normal in only 7 of these eyes.

Fig. 8 shows data for 4%-contrast solid letters. Correlation coefficients in fig. 8A and B were, respectively, 0.10 ($P = 0.5$) and 0.53 ($P = 0.0001$), indicating that, in

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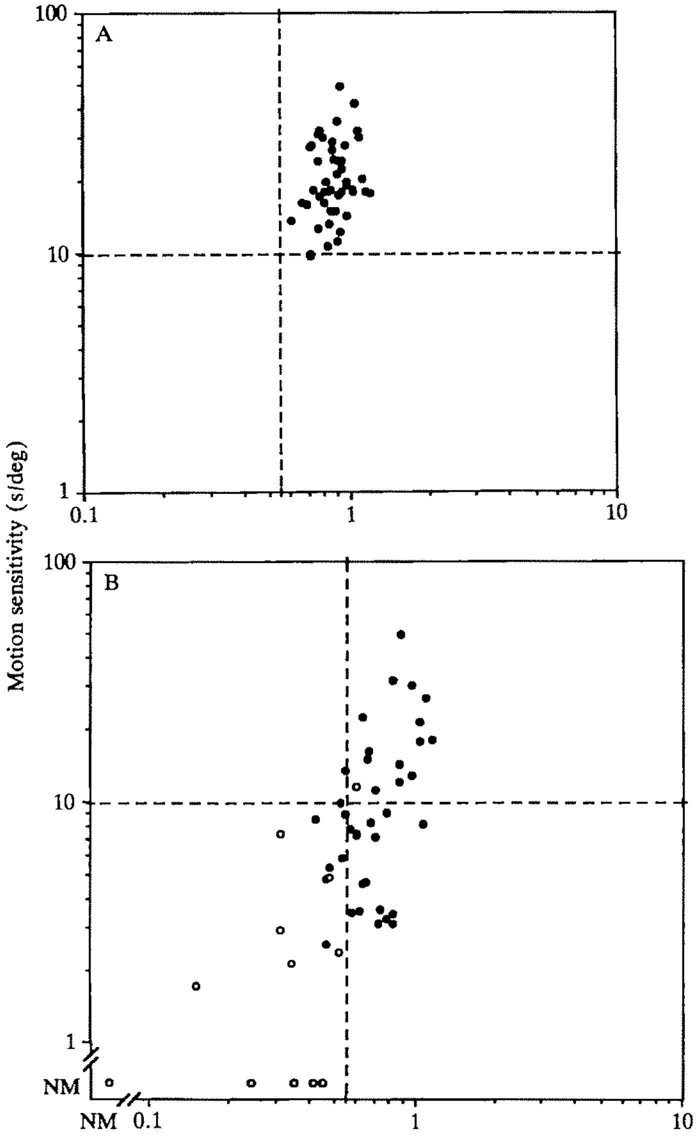

FIG 7. Sensitivity to large motion-defined dotted letters versus decimal visual acuity for isolated solid contrast-defined letter of 11%-contrast. Ordinates plot the reciprocal of the dot speed that gave 75% reading scores for dotted motion-defined letters of fixed size (50 arc min subtense, i e., 6/60 Snellen equivalent). Open circles = eyes with low Snellen acuities (>2 5 SD below the control group mean) Closed circles = normal Snellen acuity A, controls; B, patients.

patients but not in controls, there was an overall tendency for sensitivity to MD letters to be low in eyes with low acuity for contrast-defined letters. But again, as in the experiments reported above, the two measures were quite dissociated in some eyes of the patient group. Our main finding was that 20 of the 34 eyes that had low motion

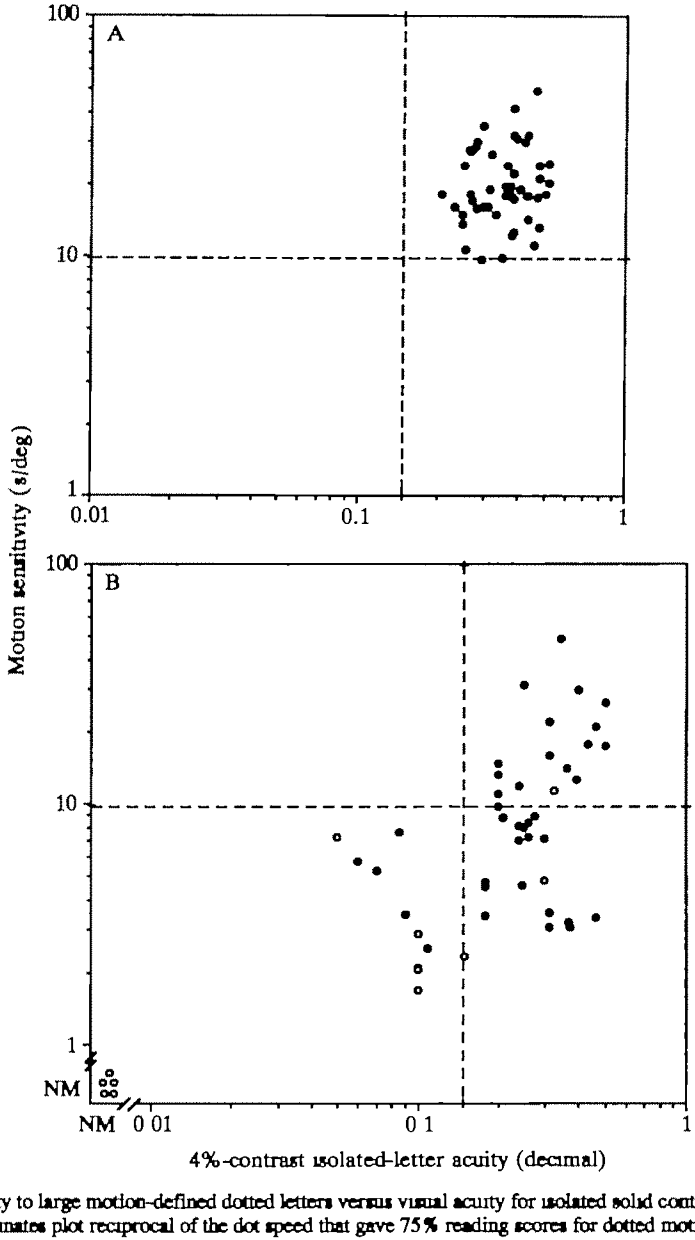

FIG. 8. Sensitivity to large motion-defined dotted letters versus visual acuity for isolated solid contrast-defined letter of 4%-contrast. Ordinates plot reciprocal of the dot speed that gave 75% reading scores for dotted motion-defined letters of fixed size (50 arc min subtense, i.e., 6/60 Snellen equivalent). Open circles = eyes with low Snellen acuities (>2 5 SD below the control group mean). Closed circles = normal Snellen acuity. A, controls; B, patients.

sensitivity for large MD letters had normal acuity for isolated, solid, 4%-contrast CD letters, and that only 2 of these 20 eyes had abnormal Snellen acuity (open circles). Conversely, none of the 14/50 eyes with low acuity for isolated, solid, 4%-contrast CD letters had normal motion sensitivity for large MD dotted letters. In 14 eyes the two measures were both abnormal, and Snellen acuity was normal in only 5 of these eyes.

Isolated letters of high, intermediate and low contrasts: interocular differences

Several visual measures, including Snellen acuity, contrast sensitivity, low-contrast acuity and evoked potential delay show a closer correlation between the left and right eye of individual control subjects than between single eyes of different control subjects. This tight correlation between vision in the left and right eyes of control subjects means that abnormality in patients with unilateral involvement could be detected with greater sensitivity by comparing interocular differences for patients and controls rather than by comparing data for individual eyes. In a certain sense, this approach causes each patient to act as his or her own control (Halliday *et al.*, 1973; Milner *et al.*, 1974; Regan *et al.*, 1976, 1977). A caveat is that interocular comparisons alone are not sufficient as they fail to detect abnormality in patients whose left and right eyes are affected similarly: for this reason interocular measures must be supplemented with monocular measures.

The correlation coefficient between the interocular ratio of speed thresholds for MD letters and the interocular ratio for normalized acuity for 11%-contrast letters was 0.21 ($P = 0.14$) for control subjects and 0.55 ($P = 0.006$) for patients. Corresponding data for 4%-contrast charts were 0.19 ($P = 0.18$) and 0.06 ($P = 0.08$). These data indicate that, in control subjects and patients, the interocular ratio for MD letter speed thresholds provides complementary information to that provided by the interocular ratio of either 11%-contrast or 4%-normalized acuities.

Overall, however, interocular ratios were considerably less sensitive to visual loss than were monocular measures. In particular, the numbers of patients with abnormal interocular ratios were as follows: 8/25 for dotted MD letter motion sensitivity, 4/25 for dotted letter acuity; 10/25 for Snellen acuity; and 3/25 and 5/25 respectively for normalized acuity for 11%-contrast and 4%-contrast isolated solid letters.

Motion sensitivity for large motion-defined letters versus Snellen acuity

Fig. 9 compares motion sensitivity for large MD letters with conventional Snellen (i.e., line acuity). Correlation coefficients in fig. 9A and B were, respectively, 0.38 ($P = 0.007$) and 0.73 ($P = 0.0001$) indicating that, in controls as well as in patients, there was an overall tendency for MD letter motion sensitivity to be low in eyes with low Snellen acuity. However, as in the experiments reported above, there was a clear dissociation between the two measures in several eyes of the patient groups. In particular, of the 34/50 eyes with abnormal motion sensitivity for large dotted MD letters, 23 had Snellen acuities within the normal range (filled circles). The converse pattern of loss was much rarer. Of the 12/50 eyes with abnormal Snellen acuity, only 1 had normal motion sensitivity for dotted MD letters.

Appendix 2 summarizes the results of all 7 tests on 50 eyes of the 25 patients.

DISCUSSION

Implications for the differential diagnosis of MS

The several diagnostic schemes that have been proposed for the differential diagnosis of MS have in common the requirement that at least two independent lesions of the

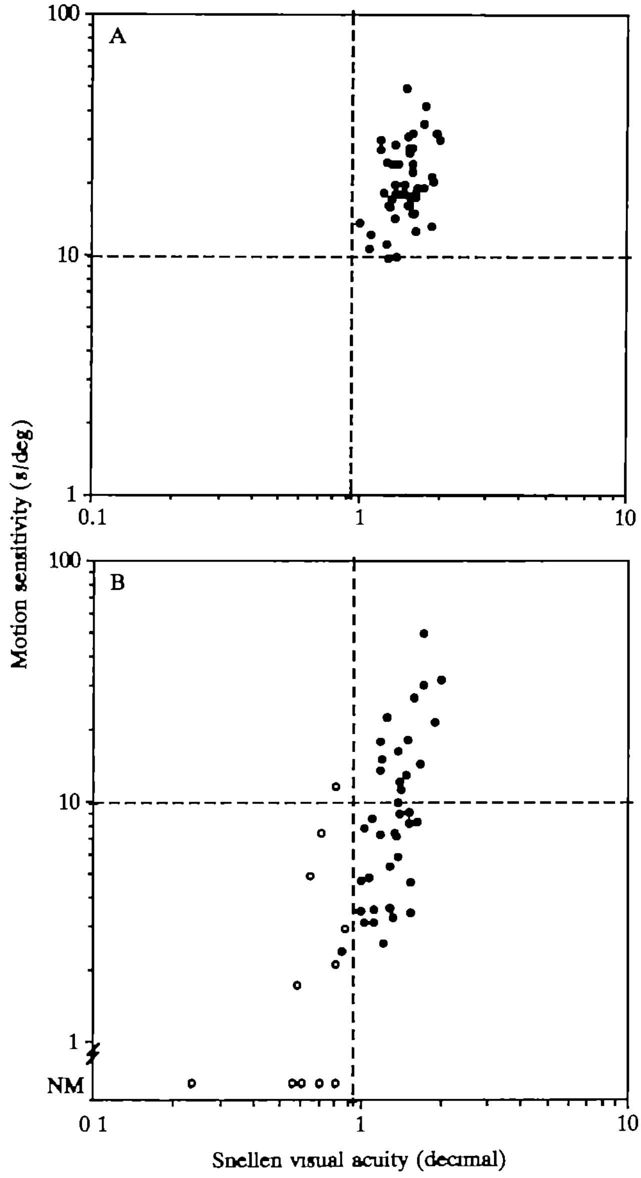

FIG. 9. Sensitivity to large motion-defined dotted letters versus visual acuity measured with the Snellen chart illustrated in fig. 3D. Ordinates plot the reciprocal of the dot speed that gave 75% reading scores for dotted motion-defined letters of fixed size (50 arc min subtense, i e , 6/60 Snellen equivalent) Open circles = eyes with low Snellen acuities (>2.5 SD below the control group mean). Closed circles = normal Snellen acuity. A, controls; B, patients.

CNS must be demonstrated before accepting a diagnosis of 'definite', 'clinically definite' or 'probable' MS (Schumacher *et al.*, 1965; McAlpine *et al.*, 1972; McDonald, 1975; Rose *et al.*, 1976; Poser, 1984). Several laboratory tests are currently in use for detecting or confirming an occult lesion in the visual pathway of patients with normal Snellen acuity and no firm history of retrobulbar neuritis. These methods include measuring visual evoked potential delay (Halliday *et al.*, 1973; Milner *et al.*, 1974; Halliday, 1982; Regan, 1989*a*), and supplementing the Snellen test with either a sinewave grating contrast sensitivity test or low-contrast acuity chart (Regan *et al.*, 1977; Bodis-Wollner *et al.*, 1979; Zimmern *et al.*, 1979; Regan and Neima, 1983; Regan, 1988*a*, *b*). In this paper we describe a new visual test that can detect visual pathology in patients who have normal contrast sensitivity, normal Snellen acuity and normal scores on low-contrast letter charts. The equipment required consists only of a standard personal computer. The procedure requires the patient to read perfectly camouflaged letters whose visibility is created entirely by relative motion rather than to read uncamouflaged letters that are either brighter or dimmer than their surroundings as is the case with conventional tests.

We conclude that motion sensitivity and contrast sensitivity are complementary measures: of the 34/50 eyes with abnormal motion sensitivity for dotted MD letters, 12 had normal contrast sensitivity for those same dotted letters. With the exception of 1 eye, the MD letter test picked up every one of the 12/50 eyes with abnormally low Snellen acuity, and in addition a further 23 eyes whose Snellen acuities were within normal limits (fig. 9B). The 'false-positive' rate for the MD letter test was only 1/50 (the statistical expectation was 1/100).

It is known that test charts comprising low-contrast solid letters can detect visual loss in a substantial number of patients whose scores on a conventional Snellen chart fall within normal limits (Regan and Neima, 1983; Moskowitz *et al.*, 1985; Lerner *et al.*, 1986; Regan and Maxner, 1986, 1987; Drucker *et al.*, 1988; Kleiner *et al.*, 1988; Regan, 1988*a*, *b*). We therefore compared scores for MD letter acuity with scores for high, intermediate and low-contrast letters. Appendix 2 and figs 6–8 indicate that testing motion sensitivity for dotted MD letters detects more abnormal eyes (34/50) than does contrast sensitivity for the same large dotted letters (22/50) and considerably more abnormal eyes than does testing visual acuity for MD dotted letters (19/50) or visual acuity for isolated, solid letters of 96%-contrast (10/50 eyes), 11%-contrast (19/50 eyes) or 4%-contrast isolated solid letters (14/50 eyes).

To compare test results for MD letters with test results for one other test, as just described, is valid providing that, as in our case, both tests have the same statistical definition of 'abnormal' (here 2.5 SD). However, it is not valid, and indeed unfair to compare test results for MD letters with each of several other independent tests and to accept a failure on *any one* of these other tests as of equal weight to a failure on the one MD letter test. Nevertheless, the MD letter test rated well on this unfair kind of comparison. (Results on high and low-contrast letters are known to be independent in many patients with MS (Regan and Neima, 1983; Regan and Maxner, 1986).) Of the 34/50 eyes with low motion sensitivity for large MD dotted letters, 14 were normal on all the following tests: Snellen acuity and isolated-letter acuity for 96%-contrast, 11%-contrast and 4%-contrast letters.

We conclude that motion sensitivity for large MD letters is more sensitive to demyelinating pathophysiology in patients with MS and ON than is contrast sensitivity for large dotted letters, more sensitive than acuity for MD letters, more sensitive than acuity for isolated, solid high, intermediate or low-contrast letters and considerably more sensitive than is the Snellen test.

On the other hand, there is no reason to suppose that an abnormal test result will prove to be specific to MS. Certainly, a delayed VEP or abnormal score on low-contrast acuity charts is not specific to MS (Carroll *et al.*, 1982; Blumhardt, 1985; Regan, 1988*a*, 1989*a*). Nevertheless, the simplicity and low cost of the MD letter test may prove to be useful as an aid to the diagnosis of MS by providing evidence for an occult 'second lesion' (McAlpine *et al.*, 1972; Poser, 1984). But perhaps the chief value of this test will prove to be in research on the mechanisms of MS by providing a further means of comparing visual abnormalities in human patients with our emerging knowledge of functional neuroanatomy and neurochemistry in the visual pathway of the nonhuman primate.

Selective blindess for motion

Although selective blindness for motion-in-depth is rather common (Regan and Beverley, 1973; Regan *et al.*, 1986; Hong and Regan, 1989), selective blindness for frontal plane motion is rare (Zihl *et al.*, 1983) although, according to Teuber *et al.* (1960), a *nonselective* depression of sensitivity to motion is often associated with cerebral hemisphere pathology. In contrast to previous studies we find a high incidence of abnormal processing of frontal plane motion: a total of 34/50 eyes had abnormal speed thresholds for reading MD letters. The most likely explanation for this apparent conflict is that only the ability to detect the presence of motion was tested in previous clinical studies, whereas we required patients to extract spatial form from motion. Recognizing motion-defined form demands more than the ability to detect the presence of motion. For example, in our test, rather than stimulating the eye with one velocity at a time, two equal and opposite speeds are present simultaneously at different locations. In order to see the letter at all the brain must contain neurons that respond, not only to the presence of motion, but also to the direction of motion and, in addition, are sensitive to the variation of velocity with distance across the retina. Furthermore, because the subject is required to read the letters rather than merely detect their presence, the test requires that the visual pathway contains neurons sensitive to the *shape* of the motion-defined letter. We will return to this point below.

In 5/50 eyes of our patient group the central visual field was effectively blind to motion in the sense that reading scores remained at chance or near-chance levels for MD letters with the highest relative dot speed that we could achieve. The highest speed of 0.9 deg/s was 8.3 times the mean speed threshold for the control group, and 21 SDs above this mean speed threshold for the control group. Motion blindness in 4 of these eyes could not be attributed to degraded Snellen acuity.

Physiological implications: different neural subsystems for processing objects defined by velocity difference and objects defined by luminance difference

An object that exactly matches its surroundings in luminance, texture and colour merges into those surroundings and cannot be seen if binocular depth cues are unavailable. Such an object is said to be perfectly camouflaged. Animals who rely on camouflage to catch their prey or to hide from their predators are adept at maintaining absolute stillness, because movement would break their camouflage and reveal them to an observing eye. The commonplace observation that objects exist that cannot be seen by a human observer so long as they remain stationary, yet spring into visibility when they move relative to the surroundings indicates that the human visual pathway is capable of detecting and also recognizing objects whose boundaries are defined exclusively by relative motion. Although this is a special kind of spatial vision, its properties can be described by equations that are formally analogous to those that describe the familiar kind of spatial vision for objects whose boundaries are defined by luminance difference (Regan, 1991).

Considering first the detection of an MD object, spatial summation extends over a greater area and temporal summation extends over a longer duration than for a solid, contrast-defined object (Regan and Beverley, 1984). However, the human visual pathway is capable of a great deal more than merely detecting a camouflaged MD object: normally-sighted subjects can also recognize MD objects, and can discriminate small differences in shape and other spatial features. For example, vernier acuity for MD dotted bars is as good as for CD dotted bars (Regan, 1986); orientation discrimination for an MD dotted bar is, at about 0.5°, comparable with the best discrimination reported in the literature for bright lines or CD gratings (Regan, 1989*b*); shape discrimination is approximately the same for MD dotted rectangles and for CD uncamouflaged rectangles (Regan, 1991; Regan and Hamstra, 1990, 1991).

It may be useful to think of the effect of dot speed on the visual perception of MD targets and the effect of contrast on the visual perception of CD targets as properties of two different physiological processes, either of which can support spatial vision. Fig. 4 and Appendix 2 present evidence that these two processes are sufficiently different at the physiological level that they can be differentially damaged. Fourteen eyes had abnormal speed thresholds for large (6/60) dotted MD letters, yet had normal contrast thresholds for 6/60 dotted CD letters, and 2 eyes showed the converse pattern of loss. This comparison between MD and CD letters is quite direct because the letters were identical in all other respects including dottiness and size. Although the comparison is less unequivocal we can also compare test results for dotted MD letters and for solid CD letters. Of 50 eyes of patients, 14 had abnormal speed thresholds for 6/60 dotted MD letters but were within normal limits on Snellen acuity, and also within normal limits on acuity for isolated letters of 96%, 11% and 4%-contrast.

A pathophysiological basis for low reading scores for motion-defined letters

We suggest here that the organization and properties of neurons in monkey areas MT and MST are consistent with the spatial discrimination of motion-defined form and that, while accepting that the detection and discrimination of forms defined by luminance contrast is largely mediated by the 'form and colour' pathway of fig. 2, the 'motion' pathway is important for detection and discrimination of motion-defined form. In particular, area MT in monkey contains a columnar system for the axis of stimulus motion (Burkhalter *et al.*, 1981; Albright *et al.*, 1984). Although MT receives a direct projection from V1 in addition to projections via V2 and V3, no such columnar organization for motion exists for V1. However, the columnar organization for motion in MT bears a formal resemblance to the well-known organization of orientation columns in V1 that have been implicated in the detection and discrimination of contrast-defined form. We suggest here that this columnar organization in MT might provide a basis for detecting motion-defined edges. Because local retinotopic organization within MT is highly systematic (Gattass and Gross, 1981; Albright and Desimone, 1987), this same columnar organization could also provide a basis for encoding precisely the relative locations of these motion-defined edges. It may be relevant here that, as well as being tuned to the direction of motion, a preponderance of monkey MT cells are also tuned to the orientation of a form (Albright, 1984).

We suggest that the selectivity of visual loss in 14 eyes that showed degraded motion sensitivity for reading 6/60 dotted MD letters with spared contrast sensitivity for 6/60 dotted CD letters can be attributed to selective dysfunction of neurons sensitive to MD edges, and that the responsible pathology was chiefly in a pathway that originates in large retinal ganglion cells, passes through the magnocellular layers of the LGN, includes homologues of cortical areas MT and MST, and is involved in processing motion. This selective damage would not necessarily be restricted to the human equivalents of MT and MST but might also include neurons sensitive to MD objects in the more distal cortical areas that project to MT.

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OFFER

A few duplicates of the floppy disc that allows the test to be run on an IBM PC are available from D.R. gratis to researchers for a small charge to cover the cost of mailing and materials.

REFERENCES

Albright TD (1984) Direction and orientation selectivity of neurons in visual area MT of the macaque. *Journal of Neurophysiology*, **52**, 1106–1130.

Albright TD, Desimone R, Gross CG (1984) Columnar organization of directionally selective cells in visual area MT of the macaque. *Journal of Neurophysiology*, **51**, 16–31.

Albright TD, Desimone R (1987) Local precision of visuotopic organization in the middle temporal area (MT) of the macaque. *Experimental Brain Research*, **65**, 582–592.

Allman JM, Kaas JH (1971) Representation of the visual field in striate and adjoining cortex of the owl monkey (*Aotus trivirgatus*). *Brain Research, Amsterdam*, **35**, 89–106.

Allman JM, Kaas JH (1974*a*) The organization of the second visual area (VII) in the owl monkey: a second order transformation of the visual hemifield. *Brain Research, Amsterdam*, **76**, 247–265.

Allman JM, Kaas JH (1974*b*) A crescent-shaped cortical visual area surrounding the middle temporal area (MT) in the owl monkey (*Aotus trivirgatus*). *Brain Research, Amsterdam*, **81**, 199–213.

Allman JM, Kaas JH (1975) The dorsomedial cortical visual area: a third tier area in the occipital lobe of the owl monkey (*Aotus trivirgatus*). *Brain Research, Amsterdam*, **100**, 473–487.

Allman JM, Kaas JH (1976) Representation of the visual field on the medial wall of occipital-parietal cortex in the owl monkey. *Science*, **191**, 572–575.

Allman J, Miezin F, McGuinness E (1985) Stimulus specific responses from beyond the classical receptive field: neurophysiological mechanisms for local-global comparisons in visual neurons. *Annual Review of Neuroscience*, **8**, 407–430.

Blumhardt LD (1985) Non-specific abnormalities of the pattern visual evoked responses (PVER) in optic neuropathy. In: *Sensory Evoked Potentials*, Volume 3. Edited by A. Starr. Milan: Edizone Technische, pp. 67–78.

Bodis-Wollner I, Hendley CD, Mylin LH, Thornton J (1979) Visual evoked potentials and the visuogram in multiple sclerosis. *Annals of Neurology*, **5**, 40–47.

BRAAK H (1980) *Architectonics of the Human Telencephalic Cortex. Studies of Brain Function*, Volume 4 Berlin: Springer.

BRINDLEY GS, LEWIN WS (1968) The sensations produced by electrical stimulation of the visual cortex. *Journal of Physiology, London*, **196**, 479–493.

BRODMANN K (1908) Beitrage zur histologischen Lokalisation des Grosshirnrinde. VI Mitteilung: Die Cortexgliederung des Menschen. *Journal of Psychology and Neurology*, **10**, 231–246.

BRODMANN K (1914) Physiologie des Gehirns. In: *Neue Deutsche Chirurgie*. Edited by P. von Bruns. Stuttgart: Enke, pp. 385–426.

BURKHALTER A, VAN ESSEN DC, MAUNSELL JHR (1981) Patterns of 2-deoxyglucose labeling in extrastriate visual cortex of unstimulated and unidirectionally stimulated macaque monkeys. *Society for Neuroscience Abstracts*, **7**, 172.

CARROLL WM, HALLIDAY AM, KRISS A (1982) Improvements in the accuracy of pattern visual evoked potentials in the diagnosis of visual pathway disease. *Neuro-ophthalmology*, **2**, 237–253.

DAMASIO AR, BENTON AL (1979) Impairment of hand movements under visual guidance *Neurology, New York*, **29**, 170–174.

DAMASIO A, YAMADA T, DAMASIO H, CORBETT J, MCKEE J (1980) Central achromatopsia: behavioral, anatomic, and physiologic aspects. *Neurology, New York*, **30**, 1064–1071.

DANIEL PM, WHITTERIDGE D (1961) The representation of the visual field on the cerebral cortex in monkeys. *Journal of Physiology, London*, **159**, 203–221.

DESIMONE R, SCHEIN SJ, MORAN J, UNGERLEIDER LG (1985) Contour, color and shape analysis beyond the striate cortex. *Vision Research*, **25**, 441–452.

DESIMONE R, UNGERLEIDER LG (1986) Multiple visual areas in the caudal superior temporal sulcus of the macaque. *Journal of Comparative Neurology*, **248**, 164–189.

DE VALOIS RL, ALBRECHT DG, THORELL LG (1982) SPATIAL FREQUENCY SELECTIVITY OF CELLS IN MACAQUE VISUAL CORTEX. *Vision Research*, **22**, 545–559.

DE YOE EA, VAN ESSEN DC (1988) CONCURRENT PROCESSING STREAMS IN MONKEY VISUAL CORTEX *Trends in Neuroscience*, **11**, 219–226.

DRUCKER MD, SAVINO PJ, SERGOTT RC, BOSLEY TM, SCHATZ NJ, KUBILIS PS (1988) Low-contrast letter charts to detect subtle neuropathies. *American Journal of Ophthalmology*, **105**, 141–145.

FLOM MC, WEYMOUTH FW, KAHNEMAN D (1963) Visual resolution and contour interaction. *Journal of the Optical Society of America*, **53**, 1026–1032.

FRANCE TD, FRANCE LW (1988) Low-contrast visual acuity cards in pediatric ophthalmology. *Graefe's Archive for Clinical and Experimental Ophthalmology*, **226**, 158–160.

GATTASS R, GROSS CG (1981) Visual topography of striate projection zone (MT) in posterior superior temporal sulcus of the macaque. *Journal of Neurophysiology*, **46**, 621–638.

GLASSMAN RB (1978) The logic of the lesion experiment and its role in the neural sciences. In: *Recovery from Brain Damage: Research and Theory*. Edited by S. Finger. New York and London: Plenum Press, pp. 3–31.

GLICKSTEIN M, WHITTERIDGE D (1987) Tatsuji Inouye and the mapping of the visual fields on the human cerebral cortex. *Trends in Neurosciences*, **10**, 350–353.

HALLIDAY AM (1982) *Evoked Potentials in Clinical Testing*. Edinburgh: Churchill Livingstone.

HALLIDAY AM, MCDONALD WI, MUSHIN J (1973) Visual evoked response in diagnosis of multiple sclerosis. *British Medical Journal*, **4**, 661–664.

HOLLIDAY IE, RUDDOCK KH (1983) Two spatio-temporal filters in human vision: 1. Temporal and spatial frequency response characteristics. *Biological Cybernetics*, **47**, 173–190

HOLMES G (1919) The cortical localization of vision. *British Medical Journal*, **2**, 193–199.

HONG X, REGAN D (1989) Visual field defects for unidirectional and oscillatory motion in depth *Vision Research*, **29**, 809–819.

HUBEL DH, WIESEL TN (1977) Functional architecture of macaque monkey visual cortex. *Proceedings of the Royal Society of London, B*, **198**, 1–59

JOHNSTON TB, WHILLIS J (1954) *Gray's Anatomy*. Thirty-first edition. London: Longman's, Green.

KLEINER RC, ENGER C, ALEXANDER MF, FINE SL (1988) Contrast sensitivity in age-related macular degeneration. *Archives of Ophthalmology*, **106**, 55–57.

LERNER B, AUER C, ALEXANDER M, RUBIN G, FINE SL (1986) Macular dysfunction after resolution of central serous chorioretinopathy. *Investigative Ophthalmology and Visual Science*, **27**, Supplement, 21.

LISBERGER SG, MORRIS EJ, TYCHSEN L (1987) Visual motion processing and sensory-motor integration for smooth pursuit eye movements. *Annual Review of Neuroscience*, **10**, 97–129.

LIVINGSTONE MS, HUBEL DH (1984) Anatomy and physiology of a color system in the primate visual cortex. *Journal of Neuroscience*, **4**, 309–356.

LIVINGSTONE MS, HUBEL DH (1987) Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *Journal of Neuroscience*, **7**, 3416–3468.

MCALPINE D, LUMSDEN CE, ACHESON ED (1972) *Multiple Sclerosis: A Reappraisal.* Second edition. Edinburgh: Churchill Livingstone.

MCDONALD WI (1975) What is multiple sclerosis? Clinical criteria for diagnosis. In: *Multiple Sclerosis Research.* Edited by A. N. Davison, J. H. Humphrey, A. L. Liversedge, W. I. McDonald and J. S. Porterfield. London: HM Stationary Office, pp. 1–8.

MAUNSELL JHR, VAN ESSEN DC (1983) Functional properties of neurons in middle temporal visual area of the macaque monkey. I. Selectivity for stimulus direction, speed, and orientation. *Journal of Neurophysiology*, **49**, 1127–1147.

MAUNSELL JHR, NEWSOME WT (1987) Visual processing in monkey extrastriate cortex. *Annual Review of Neuroscience*, **10**, 363–401.

MERIGAN WH, ESKIN TA (1986) Spatio-temporal vision of macaques with severe loss of P_β retinal ganglion cells. *Vision Research*, **26**, 1751–1761.

MILNER BA, REGAN D, HERON JR (1974) Differential diagnosis of multiple sclerosis by visual evoked potential recording. *Brain*, **97**, 755–772.

MOSKOWITZ A, SOKOL S, BARDENSTEIN D, SCHWARTZ B (1985) Performance of ocular hypertension and glaucoma patients on high and low contrast letter charts *Investigative Ophthalmology and Visual Science*, **26**, Supplement, 225.

MOVSHON JA, ADELSON EH, GIZZI MS, NEWSOME WT (1985) The analysis of moving visual patterns. *Experimental Brain Research*, Supplement 11, 117–151.

NEWSOME WT, WURTZ RH, DÜRSTELER MR, MIKAMI A (1985*a*) Deficits in visual motion processing following ibotenic acid lesions of the middle temporal visual area of the macaque monkey *Journal of Neuroscience*, **5**, 825–840.

NEWSOME WT, WURTZ RH, DÜRSTELER MR, MIKAMI A (1985*b*) Punctate chemical lesions of striate cortex in the macaque monkey: effect on visually guided saccades. *Experimental Brain Research*, **58**, 392–399.

PEARLMAN AL, BIRCH J, MEADOWS JC (1979) Cerebral color blindness: an acquired defect in hue discrimination. *Annals of Neurology*, **5**, 253–261.

PENFIELD W, RASMUSSEN T (1950) *The Cerebral Cortex of Man: A Clinical Study of Localization of Function.* New York: Macmillan.

PENFIELD W, JASPER H (1954) *Epilepsy and the Functional Anatomy of the Human Brain.* London: J. and A. Churchill.

POSER CM (Editor) (1984) *The Diagnosis of Multiple Sclerosis.* New York: Thieme-Stratton.

RATCLIFF G, DAVIES-JONES GAB (1972) Defective visual localization in focal brain wounds. *Brain*, **95**, 49–60.

REGAN D (1968*a*) A high frequency mechanism which underlies visual evoked potentials. *Electroencephalography and Clinical Neurophysiology*, **25**, 231–237.

REGAN D (1968*b*) Chromatic adaptation and steady-state evoked potentials. *Vision Research*, **8**, 149–158.

REGAN D (1970) Objective method of measuring the relative spectral-luminosity curve in man. *Journal of the Optical Society of America*, **60**, 856–859.

REGAN D (1972) *Evoked Potentials in Psychology, Sensory Physiology and Clinical Medicine.* London: Chapman and Hall.

REGAN D (1979) Electrical responses evoked from the human brain. *Scientific American*, **241**, No. 6, 108–117.

REGAN D (1982) Visual information channeling in normal and disordered vision. *Psychological Review*, **89**, 407–444.

REGAN D (1986) Form from motion parallax and form from luminance contrast: vernier discrimination. *Spatial Vision*, **1**, 305–318.

REGAN D (1988*a*) Low-contrast letter charts and sinewave grating tests in ophthalmological and neurological disorders. *Clinical Vision Sciences*, **2**, 235–250.

REGAN D (1988*b*) Low-contrast visual acuity test for pediatric use. *Canadian Journal of Ophthalmology*, **23**, 224–227.

REGAN D (1989*a*) *Human Brain Electrophysiology: Evoked Potentials and Evoked Magnetic Fields in Science and Medicine*. New York: Elsevier.

REGAN D (1989*b*) Orientation discrimination for objects defined by relative motion and objects defined by luminance contrast. *Vision Research*, **29**, 1389–1400.

REGAN D (1989*c*) *Regan Low Contrast Acuity Charts*. Lower Sackville, Nova Scotia: Paragon.

REGAN D (1990) To what extent can visual deficits caused by multiple sclerosis be understood in terms of parallel processing? *Research Publications: Association for Research in Nervous and Mental Disease*, **67**, 317–329.

REGAN D (1991) Spatial vision for objects defined by colour contrast, binocular disparity and motion parallax. In: *Spatial Vision*. Edited by D. Regan. London: Macmillan, pp. 135–178.

REGAN D, BEVERLEY KI (1973) Electrophysiological evidence for existence of neurones sensitive to direction of depth movement. *Nature, London*, **246**, 504–506.

REGAN D, MILNER BA, HERON JR (1976) Delayed visual perception and delayed visual evoked potentials in the spinal form of multiple sclerosis and in retrobulbar neuritis. *Brain*, **99**, 43–66.

REGAN D, SILVER R, MURRAY JT (1977) Visual acuity and contrast sensitivity in multiple sclerosis—hidden visual loss: an auxiliary diagnostic test. *Brain*, **100**, 563–579.

REGAN D, NEIMA D (1983) Low-contrast letter charts as a test of visual function. *Ophthalmology*, **90**, 1192–1200.

REGAN D, BEVERLEY KI (1984) Figure-ground segregation by motion contrast and by luminance contrast. *Journal of the Optical Society of America, A*, **1**, 433–442.

REGAN D, ERKELENS CJ, COLLEWIJN H (1986) Visual field defects for vergence eye movements and for stereomotion perception. *Investigative Ophthalmology and Visual Science*, **27**, 806–819.

REGAN D, MAXNER C (1986) Orientation-dependent loss of contrast sensitivity for pattern and flicker in multiple sclerosis. *Clinical Vision Sciences*, **1**, 1–23.

REGAN D, MAXNER C (1987) Orientation-selective visual loss in patients with Parkinson's disease. *Brain*, **110**, 415–432.

REGAN D, HAMSTRA S (1990) Shape and orientation discrimination for motion-defined and contrast-defined objects: temporal integration. *Investigative Ophthalmology and Visual Science*, **31**, Supplement, 524.

REGAN D, HAMSTRA S (1991) Shape discrimination for motion-defined objects: squareness is special. *Perception*. In press.

REGAN D, HONG XH (1990) Visual acuity for optotypes made visible by relative motion. *Optometry and Vision Science*, **67**, 49–55.

ROSE AS, ELLISON GW, MYERS LW, TOURTELLOTTE WW (1976) Criteria for the clinical diagnosis of multiple sclerosis. *Neurology, Minneapolis*, **26**, Supplement, 20–22.

SALTZMAN CD, BRITTEN KH, NEWSOME WT (1990) Microstimulation of visual area MT influences perceived direction of motion. *Investigative Ophthalmology and Visual Science*, **31**, Supplement, 328.

SCHAPERO M (1971) *Amblyopia*. Philadelphia: Chilton.

SCHILLER PH (1986) The central visual system. *Vision Research*, **26**, 1351–1386.

SCHUMACHER GA, BEEBE G, KIBLER RF, KURLAND LT, KURTZKE JF, MCDOWELL F *et al.* (1965) Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials of therapy in multiple sclerosis. *Annals of the New York Academy of Sciences*, **122**, 552–568.

SERENO MI, MCDONALD CT, ALLMAN JM (1988) Myeloarchitecture of flat-mounted human occipital lobe: possible location of visual area MT. *Society for Neuroscience Abstracts*, **14**, 1122.

SHAPLEY R, KAPLAN E, SOODAK R (1981) Spatial summation and contrast sensitivity of X and Y cells in the lateral geniculate nucleus of the macaque. *Nature, London*, **292**, 543–545.

SHIPP S, ZEKI S (1985) Segregation of pathways leading from area V2 to areas V4 and V5 of macaque monkey visual cortex. *Nature, London*, **315**, 322–325.

SOKOLOFF L (Editor) (1985) *Brain Imaging and Brain Function. Research Publications: Association for Research in Nervous and Mental Disease*, Volume 63. New York: Raven Press.

SPALDING JMK (1952) Wounds of the visual pathway: Part 1: the visual radiation. *Journal of Neurology, Neurosurgery and Psychiatry*, **15**, 99–107.

Sturr JF, Schultz DA, Taub HA, Hoepner JA (1989) A comparison of three clinical tests of contrast sensitivity. *Investigative Ophthalmology and Visual Science*, **30**, Supplement, 406.

Talbot SA, Marshall WH (1941) Physiological studies on neural mechanisms of visual localization and discrimination. *American Journal of Ophthalmology*, **24**, 1255–1264.

Teuber H-L (1960) Perception. In: *Handbook of Physiology*, Section 1, Volume 3. Edited by J. Field, H. W. Magoun and V. E. Hall. Washington: American Physiological Society, pp. 1595–1668.

Teuber H-L, Battersby WS, Bender MB (1960) *Visual Field Defects after Penetrating Missile Wounds of the Brain*. Cambridge, MA: Harvard University Press.

Tigges J, Tigges M (1985) Subcortical sources of direct projections to visual cortex. In: *Cerebral Cortex*, Volume 3. Edited by A. Peters and E. G. Jones. New York and London: Plenum Press, pp. 351–378.

Tweel LH van der, Spekreijse H (1969) Signal transport and rectification in the human evoked-response system. *Annals of the New York Academy of Sciences*, **156**, 678–695.

Ungerleider LG, Mishkin M (1982) Two cortical visual systems. In: *Analysis of Visual Behavior*. Edited by D. J. Ingle, M. A. Goodale and R. J. W. Mansfield. Cambridge, MA: MIT Press, pp. 549–586.

Van Essen DC (1985) Functional organization of primate visual cortex. In: *Cerebral Cortex*, Volume 3. Edited by A. Peters and E. G. Jones. New York and London: Plenum Press, pp. 259–329.

Van Essen DC, Maunsell JHR, Bixby JL (1981) The middle temporal visual area in the macaque: myeloarchitecture, connections, functional properties and topographic organization. *Journal of Comparative Neurology*, **199**, 293–326.

Woolsey CN (1971) Comparative studies on cortical representation of vision. *Vision Research*, Supplement 3, 365–382.

Zeki SM (1969) Representation of central visual fields in prestriate cortex of monkey. *Brain Research, Amsterdam*, **14**, 271–291.

Zeki SM (1971) Cortical projections from two prestriate areas in the monkey. *Brain Research, Amsterdam*, **34**, 19–35.

Zeki SM (1973) Colour coding in rhesus monkey prestriate cortex. *Brain Research, Amsterdam*, **53**, 422–427.

Zeki SM (1974) Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *Journal of Physiology, London*, **236**, 549–573.

Zeki SM (1980) The response properties of cells in the middle temporal area (MT) of owl monkey visual cortex. *Proceedings of the Royal Society of London, B*, **207**, 239–248.

Zeki SM (1983) The distribution of wavelength and orientation selective cells in different areas of monkey visual cortex. *Proceedings of the Royal Society of London, B*, **217**, 449–470.

Zihl J, Cramon D von, Mai N (1983) Selective disturbance of movement vision after bilateral brain damage. *Brain*, **106**, 313–340.

Zimmern RL, Campbell FW, Wilkinson IMS (1979) Subtle disturbances of vision after optic neuritis elicited by studying contrast sensitivity. *Journal of Neurology, Neurosurgery and Psychiatry*, **42**, 407–412.

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APPENDIX 1. CLINICAL DATA ON CASES 1–25

Case no.	*Age (yrs)*	*Sex*	*Diagnosis and date*	*VA R (decimal)*	*VA L (decimal)*	*Clinical data*
1	38	F	Definite (1986)	1.3	1.2	RBN L; +VEPs; −CT scan; +oligoclonal banding; Uhthoff's sign; ataxia
2	42	F	Definite (1984)	1.1	1.2	OA R and L; paraesthesia; ataxia; spasticity

Appendix 1 (*continued*)

Case no.	*Age (yrs)*	*Sex*	*Diagnosis and date*	*VA R (decimal)*	*VA L (decimal)*	*Clinical data*
3	40	F	Possible	1.7	1.9	ON R and L; paraesthesia
4	42	F	Definite	1.4	1.6	ON R; +MRI
5	46	F	Definite (1974)	0.65	1.4	OA R and L; +MRI, ataxia; Uhthoff's sign, skew deviation
6	32	F	Definite (1987)	1.1	1.3	ON L; +oligoclonal banding; +VEPs; paraesthesia
7	34	F	Optic neuritis	0.85	1.0	ON R and L, diplopia; +VEPs, −oligoclonal banding
8	39	F	Definite (1985)	1.2	1.1	INO; +MRI, paraesthesia upper limbs; ataxia
9	41	F	Definite (1975)	0.60	0.70	OA R and L; nystagmus R and L; paraesthesia; ataxia; spasticity
10	28	M	Definite (1988)	0.80	0.56	OA L; pendular nystagmus R and L; +MRI; ataxia, spasticity
11	40	F	Definite	1.4	1.5	Hemiplegia RHS, +CT scan, +EPs
12	31	F	Definite (1984)	1.7	1.7	+CT scan; +oligoclonal banding, ataxia
13	24	F	Optic neuritis	1.2	1.6	ON R; −CT scan; Uhthoff's sign R and L
14	51	F	Definite (1975)	0.82	0.88	ON R and L, ataxia; weakness
15	49	F	Definite (1988)	1.4	1.0	OA R and L; ataxia; paraesthesia; +MRI
16	25	F	Definite	2.0	0.58	ON L; +oligoclonal banding, paraesthesia lower limbs, ataxia
17	39	F	Definite (1987)	1.4	1.1	+MRI, weakness
18	42	F	Probable (1987)	1.5	1.5	OA R; Uhthoff's sign; bilateral INO
19	21	F	Optic neuritis	0.71	0.24	Repeated ON R and L; −oligoclonal banding; −CT scan; −MRI
20	30	M	Definite (1989)	1.3	1.4	ON R and L, +MRI; ataxia
21	42	M	Definite (1988)	1.2	1.6	+MRI; ataxia; paraesthesia; spasticity
22	47	F	Definite (1981)	1.3	1.6	Bilateral INO; −MRI; −oligoclonal banding; ataxia
23	52	F	Definite (1971)	1.5	1.0	Left INO; ataxia; paraesthesia

Case no	*Age (yrs)*	*Sex*	*Diagnosis and date*	*VA R (decimal)*	*VA L (decimal)*	*Clinical data*
24	46	F	Possible (1982)	1.4	0.80	ON R and L; paraesthesia, hemisensory loss
25	37	F	Definite	1.3	1.0	OA R and L; +oligoclonal banding; +BAEPs; +MRI, +CT scan; paraesthesia; ataxia

VA = visual acuity; RBN = retrobulbar neuritis; OA = optic atrophy, ON = optic neuritis; INO = internuclear ophthalmoplegia; VEP = pattern evoked potential; BAEP = brainstem auditory evoked potential; + = abnormal, − = normal R = right eye; L = left eye.

APPENDIX 2. TEST DATA FOR EYES 1−50 OF CASES 1−25*

Case no.	*Motion sensitivity*		*Contrast sensitivity*		*VAM*		*Snellen VA*		*96% IVA*		*11% IVA*		*4% IVA*	
	R	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*	*R*	*L*
1												*		
2	*	*	*	*	*	*				*	*	*		*
3														
4	*	*	*			*					*			
5	*	*					*		*		*	*		*
6	*	*									*			
7	*	*	*	*	*	*	*				*			
8	*	*												
9	*	*	*	*	*	*	*	*	*		*	*	*	*
10	*	*	*	*	*	*	*	*	*	*	*	*	*	*
11		*												
12														
13		*	*	*										
14	*	*	*	*	*	*	*	*	*	*	*	*	*	*
15	*	*		*		*					*			
16		*		*		*		*		*		*		*
17	*	*	*	*										*
18	–													
19	*	*	*	*		*	*	*	*	*	*	*	*	*
20	*		*		*						*		*	
21														
22	*	*			*									
23	*	*		*		*								*
24				*				*						
25	*	*			*	*								

* A star means that the test result was more than 2 5 SDs from the mean of the control group. Motion sensitivity = reciprocal of the dot speed for 75% correct reading score on 6/60 motion-defined letters, Contrast sensitivity = reciprocal of the dot contrast for 75% reading score on 6/60 contrast-defined dotted letters (illustrated in fig. 3c); VAM = visual acuity for motion-defined letters of fixed relative dot speed 0.9 deg/s, Snellen VA = visual acuity for the line chart illustrated in fig. 3D; 96% IVA = visual acuity for isolated solid letters of 96%-contrast illustrated in fig 3E; 11% IVA = visual acuity for isolated solid letters of 11%-contrast illustrated in fig. 3F; 4% IVA = same for 4%-contrast letters R = right eye, L = left eye

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ABSENCE OF BOTH AUDITORY EVOKED POTENTIALS AND AUDITORY PERCEPTS DEPENDENT ON TIMING CUES

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SUMMARY

An 11-yr-old girl had an absence of sensory components of auditory evoked potentials (brainstem, middle and long-latency) to click and tone burst stimuli that she could clearly hear. Psychoacoustic tests revealed a marked impairment of those auditory perceptions dependent on temporal cues, that is, lateralization of binaural clicks, change of binaural masked threshold with changes in signal phase, binaural beats, detection of paired monaural clicks, monaural detection of a silent gap in a sound, and monaural threshold elevation for short duration tones. In contrast, auditory functions reflecting intensity or frequency discriminations (difference limens) were only minimally impaired. Pure tone audiometry showed a moderate (50 dB) bilateral hearing loss with a disproportionate severe loss of word intelligibility. Those auditory evoked potentials that were preserved included (1) cochlear microphonics reflecting hair cell activity; (2) cortical sustained potentials reflecting processing of slowly changing signals; and (3) long-latency cognitive components (P300, processing negativity) reflecting endogenous auditory cognitive processes. Both the evoked potential and perceptual deficits are attributed to changes in temporal encoding of acoustic signals perhaps occurring at the synapse between hair cell and eighth nerve dendrites. The results from this patient are discussed in relation to previously published cases with absent auditory evoked potentials and preserved hearing.

INTRODUCTION

Auditory evoked potentials provide objective measures of auditory function particularly in children and neonates to allow appropriate intervention if auditory sensitivity is impaired (Hecox and Galambos, 1974; Galambos and Despland, 1980). Auditory evoked potentials also test the integrity of central auditory pathways and can assist in the diagnosis and treatment of a variety of neurological conditions (Starr and Achor, 1975; Starr, 1986). However, there are several paradoxical findings accompanying the use of auditory evoked potentials that are difficult to resolve. For example, even though auditory brainstem evoked potentials reflect the activity of auditory brainstem and peripheral structures (Buchwald and Huang, 1975; Starr and Hamilton, 1976; Møller *et al.*, 1981), some patients can lack components of auditory brainstem potentials and be without subjective, or even objective, alterations of auditory function (Cacace *et al.*, 1983; Jabbari *et al.*, 1983). Even more disconcerting is the rare patient in whom brainstem and even middle-latency auditory evoked potentials are completely absent although the stimuli

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are perceptible (Worthington and Peters, 1980; Bernard and Soulier, 1983; Satya-Murti *et al.*, 1983; Kraus *et al.*, 1984; Hildesheimer *et al.*, 1985; C. Berlin, personal communication; J. Jerger, personal communication). We have had the opportunity to analyse this latter inconsistency in detail in a patient in whom those auditory evoked potentials used for clinical assessment of auditory functions (brainstem, middle and long-latency) were absent yet who heard the click and tones used in these tests. We examined in detail both the patient's perceptual capabilities and physiological functions of the auditory system to help understand these findings.

The results showed the patient to have a marked impairment in using temporal features of acoustic stimuli for perception with a corresponding absence of those auditory evoked potentials that are sensitive to temporal cues. Other auditory evoked potentials not sensitive to temporal cues were preserved. The data are interpreted as being compatible with a deficit in the region of the hair cells and eighth nerve dendrites affecting the precision of timing of eighth nerve discharges. The results from both the present study and the previous case reports suggest that these patients may comprise a new type of auditory disorder affecting temporal auditory feature analysis.

METHODS

Clinical history

The subject of study is an 11-yr-old girl with progressive hearing loss of 4 yrs duration who had not been helped by hearing aids. The family history is negative for hearing disorders. She had particular difficulties in understanding speech and had become proficient in lip-reading. She volunteered that speakers sounded 'weird, like spacemen'. She had no tinnitus but occasionally had persisting auditory experiences lasting several seconds following exposure to loud sounds like a passing truck. We could not elicit this experience with any of the signals we used in these studies. There were no symptoms of vestibular, motor, cognitive or other sensory dysfunction. Both the general physical and neurological examinations were normal. Routine haematological and biochemical tests as well as MRI of the brain, brainstem, and eighth nerves were normal. Caloric stimulation of the labyrinths while recording eye movements revealed absent responsiveness from the right ear and reduced responsiveness from the left ear.

Clinical measures of auditory function in 1984 and 1985 (Table 1) showed a bilateral mild pure tone loss (20−40 dB) extending across all frequencies. Air conduction thresholds increased gradually with a conductive component (air-bone gap) first appearing in the left ear in 1986 and in the right ear in 1989. The air-bone gap became particularly marked in the left ear in 1989 and 1990 and tympanograms at those times demonstrated negative pressures (−250 to −450 mm H_2O). Tuning fork tests of the left ear at the 1990 examination showed that bone conduction thresholds were lower than air conduction thresholds. There was a progressive bilateral decrease in word intelligibility scores between 1984 and 1990, and performance worsened if stimulus levels were raised. In 1990, using sound fields at 70 dB SPL, the patient had difficulty distinguishing between consonant-vowel-consonant monosyllabic words differing only by their vowels, for example, 'goat, got, get or gate' (57% correct with chance performance being 25%), and was only slightly better (74% correct) when the distinguishing acoustic feature was the consonants, for example, 'tip, zip, pip or chip'. However, she always correctly identified the high frequency consonants 'ch, s, t, wh, sh'.

The patient underwent a myringotomy on the left ear in January 1990 for placement of a ventilation tube in an effort to correct the conductive deficit. At the time the middle ear was explored, no fluid was found and the ossicles were entirely mobile. The finding of a normal middle ear was surprising in light of the immediately preceding clinical audiological measures. We used the opportunity to try to assess the excitability of the eighth nerve by placing a stimulating ball electrode, insulated except for the tip, in the round window niche. Electrically stimulating between this electrode and another placed on the contralateral side of the head (100 μs/phase biphasic current pulses at 0.7 mA) did not evoke any reproducible short-latency potentials. The round window electrode was maintained in place while the tympanic membrane flap was

TABLE 1. AUDIOMETRIC TEST RESULTS (BONE CONDUCTION/AIR CONDUCTION)

Right ear Frequency (Hz)	*Dates of audiological examinations*						
	9/84	*11/85*	*6/86*	*8/87*	*2/88*	*2/89*	*1/90*
	Threshold (dB HL)						
250	NT/40	NT/10	10/20	20/30	30/35	30/45	25/55
500	NT/65	5/10	20/20	25/25	35/40	45/55	70/70
1000	NT/55	20/20	20/40	40/45	45/45	45/70	45/50
2000	NT/20	0/0	10/20	20/20	30/35	30/55	40/45
4000	NT/35	5/25	25/25	60/60	60/60	50/75	45/60
8000	NT	15	20	40	50	45	45
Speech							
SRT/SAT (dB HL)	NT	15/NT	35/NT	30/NT	50/25	45/NT	NT/55
WDS (%)	NT	NT	88	56	36	12	16
Acoustic reflex	NT	NT	Abs	Abs	NT	NT	Abs
Tympanometry (mm H_2O)	NT	NT	−250	NL	NT	−100	NL

Left ear Frequency (Hz)	*Dates of audiological examinations*						
	9/84	*11/85*	*6/86*	*8/87*	*2/88*	*2/89*	*1/90*
	Threshold (dB HL)						
250	NT/35	15/25	10/25	35/45	30/50	40/60	40/80
500	NT/35	30/40	50/50	60/80	55/55	55/105	NR/95
1000	NT/35	35/35	50/70	55/60	45/50	NR/95	60/90
2000	NT/20	20/20	15/25	30/35	20/25	NR/100	40/45
4000	NT/35	25/30	35/40	70/70	40/40	65/75	60/80
8000	NT	25	30	85	65	85	85
Speech							
SRT/SAT (dB HL)	NT	35/NT	50/35	NT/55	40/35	NT/60	NT/80
WDS (%)	NT	NT	54	NT	0	NT	8(12/89)
Acoustic reflex	NT	NT	Abs	Abs	NT	NT	Abs
Tympanometry (mm H_2O)	NT	NT	−250	−300	NT	−450	−400

NT = not tested; Abs = absent; NR = no response; NL = normal; SRT = speech reception threshold; SAT = speech awareness threshold; WDS = word intelligibility score.

replaced and the insulated electrode lead packed in the ear canal. Stimulating later that day after the patient had awoken resulted in the patient experiencing discomfort in the 'ear' or on the 'tongue' at the highest current levels without having any auditory sensations. No short-latency potentials could be recorded to these stimuli. We cannot ascertain whether the failure to evoke short-latency potentials or to elicit auditory sensations on stimulating the cochlea reflected a loss of sensitivity of the eighth nerve to electrical currents or whether the electrode had moved postoperatively from its original position in the round window niche to a position relatively remote from the cochlea.

Auditory brainstem potential testing performed by several laboratories showed either an absence of reproducible components, or only a few waves of atypical form and latencies not corresponding to normal records. On our tests, visual evoked potentials to checkerboard pattern reversal stimulation and somatosensory evoked potentials to both median and posterior tibial nerve stimulation were within normal limits.

We recorded a variety of auditory evoked potentials (*see* Table 2 for test details) on 3 occasions: March 1988, June 1988, and February 1989. The former 2 were completed before the definition of the

TABLE 2. AUDITORY EVOKED POTENTIAL RECORDING PARAMETERS

Auditory evoked potential component	*Electrode site*	*Filter window*	*Stimulus type*	*Rate of stimulation*
Cochlear microphonic	Canal-Cz	100–5000 Hz	Click or 4 kHz tone	11/s 1/s
Brainstem evoked potentials	Cz-Cvii Cz-M ipsi Cz-M contra	100–3000 Hz	Click	11/s
Frequency following response	Cz-M contra	30–3000 Hz	400 Hz	1/s
Middle-latency auditory evoked potentials	Cz-Cvii	30–500 Hz	200, 1000 and 4000 Hz tone	5/s
Long-latency auditory evoked potentials	Cz-Cvii	0.03–30 Hz	200, 1000 and 4000 Hz tone	0.5/s
Sustained DC potential	Cz-M ipsi	0.03–30 Hz	1000 Hz tone	0.4/s
Cognitive evoked potentials 1. Target detection 2. Omitted stimulus 3. Processing negativity	Fz-M linked Cz-M linked Pz-M linked Eye: above and below	0.03–17 Hz	Musical notes (middle C and high D)	0.5/s

Ipsi = ipsilateral to ear of stimulation; contra = contralateral to ear of stimulation; M = mastoid; Cvii = seventh cervical vertebra (all other electrode notations are in reference to the 10–20 system of placement).

air-bone gap in the left ear. The tests included: (1) auditory brainstem potentials (3 occasions); (2) auditory middle-latency potentials (3 occasions); (3) auditory long-latency potentials (3 occasions); (4) cochlear microphonic potentials (2/89); (5) frequency following responses (2/89); (6) sustained 'DC' cortical potentials (2/89); and (7) cognitive event-related potentials to both auditory and visual stimuli (P300 and processing negativity, 6/88, 2/89).

For cognitive evoked potentials in the auditory modality, 2 notes, middle C (fundamental of 256 Hz) and D one octave higher (fundamental of 576 Hz) comprising both the fundamental and its harmonics, were generated by a computer and presented once every 2 s via headphones for a total of 300 trials. The duration of the notes was 100 ms. The higher target note had a probability of 0.2 and was randomly intermixed with the frequent nontarget stimulus. Their intensity was 60 dB nHL, a level that was 'clear' for the patient. For the visual modality, 2 letters, 'X' (the nontarget) or 'O' (the target) were presented on a video monitor once every 2 s also for 300 trials. The subjects (2 controls with normal hearing aged 11 and 12 yrs and the patient) pressed a response button whenever the target appeared and reaction times (RT) and accuracy were measured. Evoked potentials both to the targets and nontargets not contaminated by eye movements were averaged 5 times for the patient, twice for one control, and 4 times for the second control. In the auditory modality, potentials were also recorded in a 'no task' condition using only one of the notes with the subject instructed 'not to pay attention to the stimuli and to remain awake'. For the patient and one of the controls evoked potentials were also averaged to auditory targets and nontargets during a 'visual attention' condition requiring that she read a story and later answer questions about its content. The potentials evoked to the nontargets in both the 'no task' and the 'visual attention' task were subtracted from the potentials evoked by the same stimuli during classification of the notes to provide a measure of brain potentials accompanying focused auditory attention (Näätänen, 1982). The subjects were also tested during a variant of the target detection task in which only nontarget notes were presented once every 2 s except for occasional ($P = 0.2$) and unpredictable omissions. The subject pressed a response button with each omission and averages of the brain events were made commencing at the time when the stimulus would have appeared. Potentials evoked by the absence of a stimulus are certainly cognitive in origin.

Control subjects

Up to 5 young (aged 11–17 yrs) subjects with normal hearing, 1 of whom was the patient's sister, were used in those tests for which we did not have appropriate normative data. Audiometry was normal both in the sister and the controls.

Psychophysical assessment

Psychophysical assessments of auditory function were performed on 3 occasions (3/88, 2/89, 12/89). The tests quantified perception of acoustic signals based on frequency, intensity and temporal cues. The dates of the tests are indicated below for comparison with the audiometric results.

For temporal discrimination we measured: (1) lateralization of binaural clicks as a function of interaural time and intensity disparities (3/88); (2) threshold to mask low frequency signals (masking level difference or MLD) when the binaural signals were in-phase and 180° out-of-phase (3/88); (3) perception of binaural beats and monaural physical beats with low frequency signals that differed slightly in frequency, that is, 300 and 303 Hz (3/88); (4) monaural resolution of paired clicks as a function of temporal separation (3/88); (5) resolution of paired electrical stimulation to the median nerve and to the volar surface of the middle digit (2/89); (6) monaural just noticeable differences (JNDs) for the duration of a 1000 Hz tone at 40 dB SL (2/89); (7) the relation between tone duration and monaural threshold, right ear only (12/89); and (8) monaural detection of a silent period in a tone burst as a function of the duration of the tone burst, right ear only (12/89). Those tests requiring binaural processes were carried out in 3/88 when the air conduction thresholds of the ears were comparable.

For frequency discrimination we tested monaural JNDs at 200, 500, 1000, 2000, 4000 and 8000 Hz (2/89) and for intensity discrimination monaural JNDs for tones at 20 and 40 dB SL (2/89).

Test procedures

Temporal discrimination

Binaural lateralization. TDH 49 earphones were activated with 100 μs pulses, approximately 30 dB above monaural thresholds, at a 1/s rate. Large interaural differences in intensity were first used so that the subject would experience an image that was easily lateralized to the right or the left side of the head. A systematic measure of intracranial lateralization was then made as a function of interaural time and intensity differences.

Masking level differences (MLDs). Binaural thresholds were defined to equal intensity continuous 300 Hz signals in the presence of masking noise; the latter was derived from a single generator and presented binaurally at 30 dB SL. Binaural thresholds for the low frequency tone when in-phase and when 180° out-of-phase were determined.

Binaural beats. Two low frequency tones differing slightly in frequency (e.g., 300 and 303–350 Hz) were presented one to each ear. Their intensities were the same and were not quantified beyond their being suprathreshold and of 'comfortable loudness'. The subject was first trained to appreciate the quality of this auditory percept monaurally by mixing the 2 frequencies to produce an amplitude modulated signal, that is, a physical beat, that changed in intensity at a rate equal to the frequency difference (3–50 Hz) between the 2 tones.

Monaural temporal resolution. Pairs of clicks were presented monaurally at 85 dB nHL with the temporal separation between the two clicks varying in 1 ms increments. The subject reported the signals as 'one click' or 'two clicks'. Occasional catch trials containing only a single stimulus were presented. The time separation at which the paired signals were consistently identified as 'two clicks' was the measure of monaural temporal resolution.

Somatosensory temporal resolution. Pairs of electrical pulses from a constant current stimulator were delivered to a pair of skin electrodes, 1 inch apart, placed near the median nerve at the wrist or to the volar surface of the middle finger. The pulses were 0.1 ms in duration. The intensity of the pulses to the digit was raised above sensory threshold to a level that was tolerable while the current strength for median nerve stimulation was just below that evoking contraction of the hand muscles. The stimuli were applied once every 3–4 s and the subject reported whether there were 'one' or 'two' stimuli. Initially large interstimulus intervals were employed; subsequently the interstimulus interval was reduced in 10 ms increments. Occasional catch trials having only a single stimulus were used.

Monaural stimulus duration. Pairs of 1000 Hz tones (10 ms rise and fall time, 40 dB SL) separated from each other by 500 ms were presented every 5 – 10 s. Two tone durations were tested: 50 and 500 ms. For the 50 ms duration tones, the duration of the second tone of the pair was varied in 5 ms increments and 50 ms for the 500 ms duration tones. The subject reported the signals as being either 'same' or 'different' in duration.

Monaural threshold as a function of signal duration. The threshold of 1000 Hz tone bursts, presented 1/s, was defined as a function of the signal's duration. Only the right ear was tested. Tonal durations between 200 and 5 ms were used. Threshold was measured using the method of limits: the average of an ascending and descending signal series that was varied in 2 dB steps.

Monaural gap detection. Pairs of 1000 Hz tones were presented at 117 dB nHL, a level which was reported as 'comfortably loud' by the patient. Only the right ear was tested. In the middle of one of the tone pairs, a silent interval was introduced on a random schedule. One of the tone pairs never contained a silent period. The tone pairs were separated by 500 ms. The patient was instructed to press one of two response buttons after each of the stimulus pairs; one button indicated that the gap was in the first tone and the other button indicated that the gap was in the second tone. For each duration of the tone bursts (5, 10, 20, 50, 55, 60, 80 and 200 ms) the length of the silent period was varied adaptively to achieve a 79% correct performance.

Frequency discrimination

Monaural JNDs at 200, 500, 1000, 2000 and 4000 Hz were defined. At each of these frequencies pairs of tone bursts (500 ms duration, 10 ms rise and fall times, 30 dB SL) separated by 400 ms were presented once every 5 – 10 s. The initial tone was the 'standard' and the second tone's frequency was varied. Occasional catch trials were inserted in which the 2 tone bursts were of the same frequency. The subject was asked whether the 2 tones were the 'same' or 'different' in pitch. The just noticeable difference was defined at the 100% confidence limits.

Intensity discrimination

Monaural JNDs for a 1000 Hz tone at 20 and 40 dB SL were defined. The paired stimuli were presented as for frequency JNDs and the intensity of the second stimulus varied in 1 dB increments. The subject was asked whether the 2 tones were the 'same' or 'different' in loudness.

RESULTS

Evoked potentials

Cochlear potentials

Potentials recorded from an electrode in the external ear canal referenced to the vertex revealed a series of components extending for up to 5 ms (fig. 1A) in response to clicks of 87 dB nHL, approximately 35 dB above the patient's threshold to clicks at this recording session. The potentials reversed polarity when the click was changed from condensation to rarefaction. The potentials were not obtained when the air tube coupling the transducer to the ear canal was clamped, indicating that the recordings were not artefacts of the electrical voltages applied to the transducer. The latency of these potentials did not change as signal intensity was reduced (fig. 1B) in contrast to neural components which lengthen in latency. The microphonic, rather than neural, character of these potentials was further suggested by their persistence in the presence of noise (fig. 1C) sufficient to mask the perception of the clicks (Coats and Dickey, 1970). We were surprised by the duration of the cochlear microphonic accompanying the presentation of the transient click stimulus. However, the waveform of the acoustic signal measured in a 3 cc coupler showed there to be an initial high amplitude transient followed by low amplitude acoustic energy for 5 ms, approximately the same duration as the cochlear

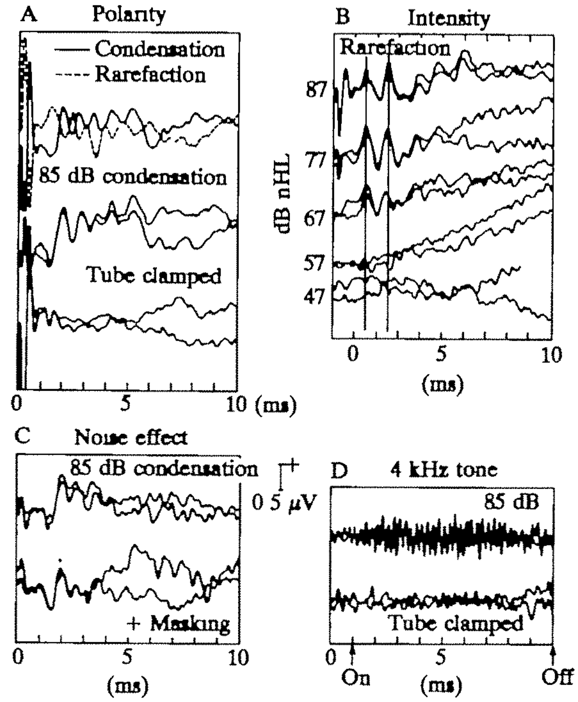

FIG. 1. Cochlear microphonic recordings (2/89) obtained from the patient between an electrode in the right ear canal referenced to the vertex. A, the early latency components reverse polarity with a change of click polarity from condensation to rarefaction These components are not artefacts of the voltages applied to the transducer since they are lost when the air tube transmitting the acoustic energy from the transducer to the ear canal was clamped. B, these potentials persist over a 30 dB intensity range, becoming smaller as intensity is reduced, without a change of latency (*see* vertical lines alignment on peaks) C, these potentials persist in the presence of a noise sufficient to mask the perception of the click. D, cochlear microphonic potentials recorded over a longer time base to a 4 kHz tone with and without masking noise.

microphonic components recorded from the ear canal electrode. Cochlear microphonics were also detected to a long duration 4 kHz tone of 87 dB nHL (fig. 1D).

Auditory brainstem potentials

Auditory brainstem evoked potentials had no identifiable components at 65 and 75 dB nHL. At both 85 and 95 dB nHL reproducible waves were recorded from only 1 of the 3 recording montages: vertex to the mastoid ipsilateral to the ear being stimulated. Reproducible waves were not obtained from the vertex to mastoid contralateral to the ear being stimulated or from the vertex to a noncephalic reference (fig. 2, 'ABR'). Right ear stimulation at 95 dB nHL showed latencies for vertex positive components at 1.1, 1.8, 2.0 and 3.2 ms. Left ear stimulation showed latencies at 1.8 and 2.6 ms. The components occurred at the same latency though at a reduced amplitude when the click intensity was reduced to 85 dB nHL. Measurement of cochlear potentials clarified that these atypical ABR components did not represent artefacts of the voltages applied to the earphones, but were reflections of cochlear microphonics detected by the electrode placed close to the stimulated ear.

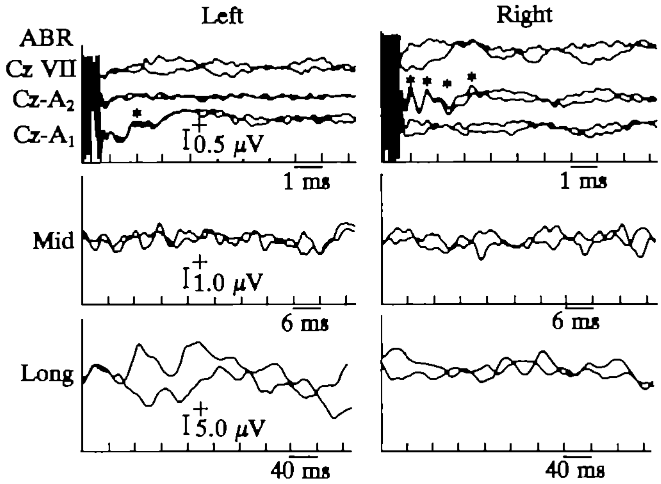

FIG. 2. Auditory brainstem (ABR), middle (mid), and long-latency (long) auditory evoked potentials recorded (3/88) from the patient to left and right ear stimulation. An asterisk is placed above reproducible components Note that for the ABR these components were only detected in the recordings between the vertex and the ear receiving the stimulus (Cz to A1 or A2) No reproducible components were found in the middle and long-latency potentials. Stimulus intensity was 95 dB nHL for the ABR and 85 dB nHL for the other recordings.

Auditory middle and long-latency potentials

On 3 separate testing dates, there were no reproducible components for either the middle or long-latency auditory evoked potentials either to clicks or tone bursts (200, 1000 and 4000 Hz) at intensities up to 95 dB nHL (fig. 2, 'Mid' and 'Long'). The stimuli were always suprathreshold in intensity. The patient was asleep during these tests. The failure to detect long-latency components on this test will be compared with the potentials obtained during the performance of an auditory target detection task (*see* 'Cognitive evoked potentials' below).

Frequency following response

No potentials were recorded that followed the microstructure of low-frequency tones.

Auditory sustained 'DC' potentials

In normal subjects a long-duration tone evokes a sustained negative shift, of maximal amplitude at the vertex, that persists for the duration of the tone (Picton *et al.*, 1978). The sustained negative shift is accompanied at its onset by N100 and P200 components (fig. 3, control). When the patient was tested for a long-duration 1000 Hz tone at an intensity of 87 dB nHL, approximately 30 dB above her threshold, a sustained negativity appeared that peaked at approximately 250 ms, almost 150 ms later than the normal latency of the N100 component. The duration of the shift lengthened as tone duration lengthened (fig. 3). The amplitude of the sustained negativity was affected by the level of arousal, being large (up to 12 μV) when she was awake and small (2–4 μV) or even undetectable when she was asleep.

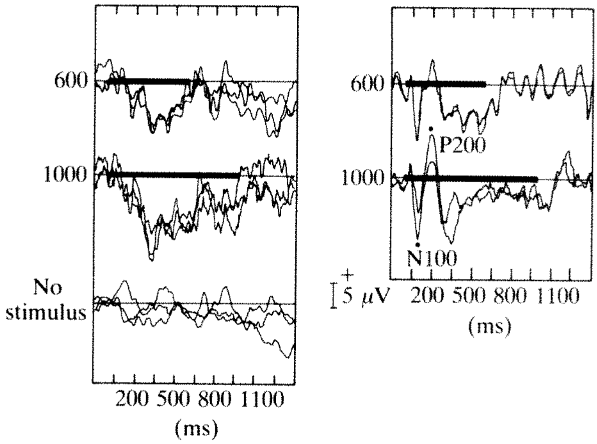

FIG. 3. Sustained potentials to long duration tone bursts presented to the right ear recorded (2/89) from the patient (*left*) and an age-matched control with normal hearing (*right*). The tone's presence is indicated by the thickening of the baseline. Note the sustained negative potential that occurs for the duration of the stimulus and the absence of the onset and offset transient components (N100, P200) in the patient but their presence in the control.

Cognitive evoked potentials

The patient's detection of target notes was accurate (96%) with only an occasional error made to the frequent nontarget tones (98% correct). Reaction times were 740 ms compared with 319 and 490 ms in 2 normal young subjects of the same age. In the patient the evoked potentials to the target notes (fig. 4A) contained a positivity (average baseline-to-peak amplitude 18.5 μV) at a latency of 513 ms, largest parietally, which was markedly attenuated to the nontargets (2.1 μV). A parietal positivity also appeared (latency 571 ms, amplitude 20.3 μV) when the task was varied to require the detection of the occasional and unpredictable absence of a regularly recurring note (fig. 4B). Comparable waveforms from 1 of the normal age-matched subjects are shown in fig. 4. Table 3 contains measures of cognitive evoked potential components and behaviour from both the patient and controls. In the target detection task P300 latencies for the controls were 320 and 344 ms with an amplitude of 28.6 and 21 μV. In the omitted stimulus task P300 latencies were 554 and 501 ms and amplitudes were 11.8 and 14.4 μV. The prolongation of both the RT and the latency of the patient's P300 in the auditory target detection task relative to the normal values cannot be attributed to a specific auditory processing difficulty since both RT and P300 latency in the visual target detection task were also delayed compared with the normals: RT was 500 ms in the patient compared with 355 ms in the control (only 1 control was tested in this task); P300 latency in the patient was 462 ms compared with 300 ms in the control.

The nontarget stimuli in these tasks also evoked a series of components. In the patient the latencies and amplitudes varied considerably (compare A, B and C in fig. 4A collected during different tasks). In the grand average of the nontargets collected during 5 repetitions of the target detection task, the components consisted of an N165 (mean of 173 ± 24 ms) and a P240 (mean of 244 ± 24 ms). The N165 was of equivalent amplitude along the midline scalp whereas the P240 was of maximal amplitude over the parietal region.

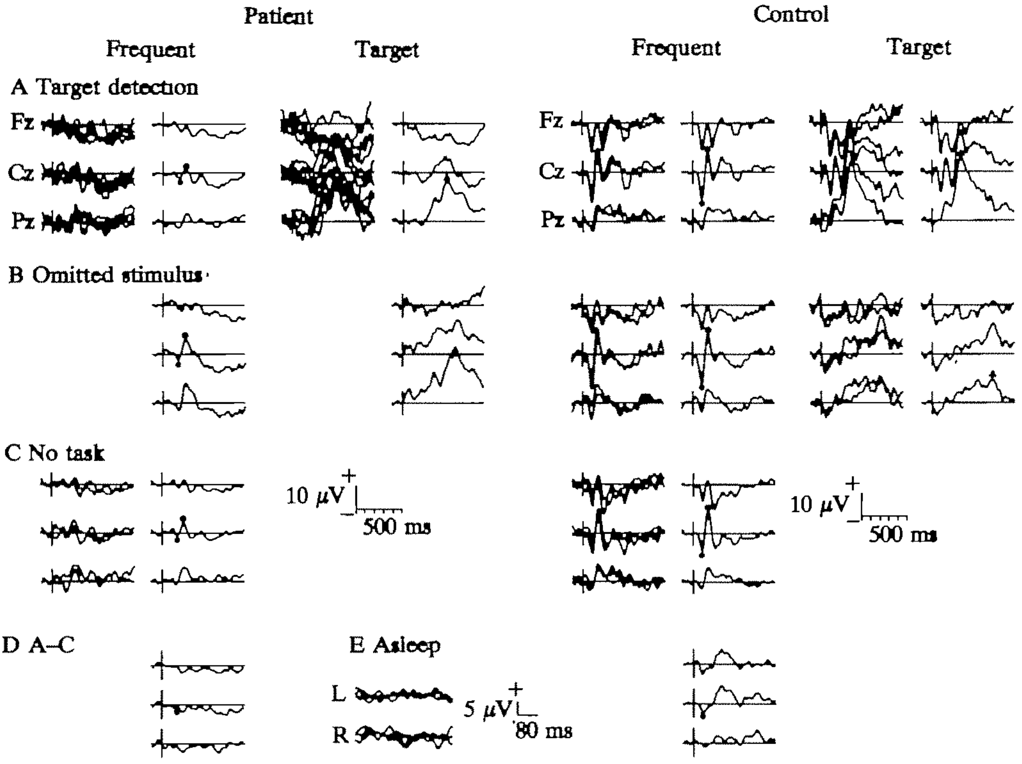

FIG 4 'Cognitive potentials recorded from Fz, Cz, Pz, referenced to linked ears in the patient (6/88 and 2/89) and a normal control (control 1 in Table 3). The potentials to 'nontargets' and to 'targets' are arranged in separate columns in different conditions. A, during performance of the target detection task; B, during performance of the omitted stimulus task; C, during a 'no task' condition; D, the difference waveforms between C and A, i.e A−C; E, long-latency evoked potentials to a 1000 Hz tone collected when the patient was asleep. The superimposed traces represent repeated averages collected in the different conditions with their grand average displayed to the right. The components are labelled by the polarity at Cz (P for positive and N for negative) and their approximate latency in ms. N160 for the patient and N100 for the control (●); P240 for the patient and P200 for the control (○); P300 for both the patient and control (△). Note the clear P300 component to the target in both the patient and the control in conditions A and B. The N160 and P240 components to the nontargets in the patient when compared with the N100 and P200 components in the controls are delayed in latency, have a different scalp distribution, and are absent when the patient is asleep.

The N165-P240 amplitudes in all the tasks ranged from 4.0 to 9.6 μV and were not present when the patient was asleep (*see* fig. 4E). The characteristics of the N100 and P200 components in the control subjects were quite different from the N160 and P240 components in the patient. In the control subjects, nontargets elicited N100 and P200 components which were of short latency (N100 at 99 and 108 ms; P200 at 163 and 144 ms) that only varied a few ms between repetitions. The N100-P200 amplitudes ranged from 16.9 to 21.3 μV for 1 of the controls and 3.2 to 7.2 μV for the other and had frontocentral maxima. In normal subjects the N100 and P200 components persist in sleep.

A sustained negative shift was identified in the patient's auditory evoked waveforms when the potentials to the nontargets collected during the performance of the tasks were subtracted from the potentials to these same stimuli when the subject was not performing

TABLE 3 COGNITIVE EVOKED POTENTIALS AND BEHAVIOUR

	Evoked potentials									
	Latency (ms)				*Amplitude (µV)*				*Behaviour*	
	N1	*P2*	*P3*	*PN*	*N1*	*P2*	*P3*	*PN*	*RT(ms)*	*Acc(%)*
Patient										
Auditory tasks										
Target (5)	173	244	513	216	−3.3	2.8	18.5	−3.4	740	96
SD	24	24	60		1.2	1.8	3.1		96	2
Omitted (1)	161	235	571		−3.2	6.4	20.3		808	100
No task (2)	163	230	419		−0.9	4.3	4.5			
SD	8	3			1.2	1.8				
Reading (1)	177	251	NM	302	−1.6	2.4	NM	−3.9		
Visual task										
Target (2)	136	181	462		−2.1	3.9	23.9		500	98
SD	3	6	28		1.9	0.1	0.9		26	2
Control 1										
Auditory tasks										
Target (2)	99	163	320	91	−11.1	8.3	28.6	−4.5	319	100
SD	0	3	25		2.3	2.7	2.6		4	
Omitted (2)	99	169	554		−12.7	8.6	11.8		485	87
SD	6	6	107		2.8	3.7	0.1		75	7
No task (3)	98	164	368		−7.3	9.6	3.4			
SD	2	8	55		2.3	0.6	1.1			
Reading	ND	ND	ND		ND	ND	ND			
Visual task										
Target	ND	ND	ND		ND	ND	ND		ND	ND
Control 2										
Auditory tasks										
Target (4)	108	144	344	232	−2.3	0.9	21.0	−5.8	490	100
SD	9	16	21		3.8	6.0	2.9		10	
Omitted (1)	106	161	501		−2.1	1.9	14.4		617	100
No task (4)	107	147	336		−1.8	2.7	4.7			
SD	2	5	9		3.6	3.4	1.4			
Reading (1)	103	161	509	NM	−8.3	−1.1	3.7			
Visual task										
Target (2)	114	188	300		2.6	2.9	18.9		355	99
SD	6	16	8		2.3	2.7	0.4		8	1

Measures are of mean and SD during several cognitive tasks described in the Methods. The number of averages comprising the measures is indicated in parentheses in the left-hand column. N1 and P2 were measured at Cz to nontargets, P3 was measured at Pz to targets; PN was measured at Fz. NM = not able to measure; ND = not done, RT = reaction time, Acc = accuracy, PN = processing negativity

the task (fig. 4D). The amplitude of the sustained negative shift was 3.4 µV, comparable with that found in normals.

Psychoacoustical studies (see Table 4)

Binaural lateralization

Intensity cues. When using simultaneously presented binaural clicks with interaural intensity disparities of >20 dB, the patient correctly lateralized the clicks to the ear with the more intense stimulus. With smaller interaural differences the probability of

TABLE 4. BEHAVIOURAL TEST RESULTS (RIGHT EAR/LEFT EAR)

	Patient		*Controls*	
Stimulus	*Frequency JND (2/89)*			
Test frequency (Hz)	dF	dF/F	dF	dF/F
250	60/86	0.24/0.34	7/10	0.03/0.04
500	71/61	0.14/0.12	13/15	0.03/0.03
1000	85/138	0.08/0.14	10/9	0.01/0.01
2000	679/784	0.33/0.39	40/47	0.02/0.02
4000	385/326	0.09/0.08	62/73	0.02/0.02
8000	1850/1043	0.23/0.13	74/81	0.01/0.01
	Intensity JND (2/89)			
Test intensity 30 dB SL	10/10 dB			3.9/3.9 dB
	Temporal cues			
Binaural tests (3/88)				
Lateralization				
Interaural time[1]	Absent		300 μs	
Interaural intensity[2]	>36 dB		7 dB	
MLD	Absent		12 dB	
Binaural beats	Absent		Present	
Monaural tests				
Paired clicks[3] (3/88)	90 ms		2–4 ms	
Duration JND (2/89)				
50 ms	30/30 ms		20/30 ms	
500 ms	300/200 ms		200/200 ms	
Gap detection (12/89)	20–80 ms		2–5 ms	
Threshold/duration[4]	40 dB		10 dB	
Somatosensory				
Paired shocks[3] (3/88)	50–60 ms		40–60 ms	

JND = just noticeable difference; dF/F = frequency shift/standard frequency; MLD = threshold shift when interaural phase changed by 180°. [1] Interaural time disparity to switch lateralization. [2] Interaural intensity disparity to switch lateralization. [3] Time separation for perceiving stimuli as paired. [4] Threshold difference between 10 and 100 ms duration tones.

lateralizing the binaural stimulus changed in a relatively smooth manner: from a probability of 0.1 when left > right by 16 dB to a probability of 0.7 when left < right by 16 dB (fig. 5A). Throughout this intensity range a high proportion of responses indicated that binaural fusion of the clicks had not occurred since she reported clicks on 'both sides'. Bilateral localization was never reported with monaural stimuli. Performance by the sister with normal hearing on the same task showed that lateralization shifted completely from 'left' to 'right' with a 7 dB interaural difference in contrast to the approximately 32 dB interaural difference for the patient. The normally hearing sister never reported 2 images simultaneously.

Time cues. With clicks of equal intensity, the normally hearing sister had a shift of lateralization over a 0.3 ms interaural time change, reporting 'left' when the click to the left ear preceded the click to the right by 0.2 ms and 'right' when the click to the left ear followed the click to the right ear by 0.1 ms (fig. 5B). Fusion of the binaural

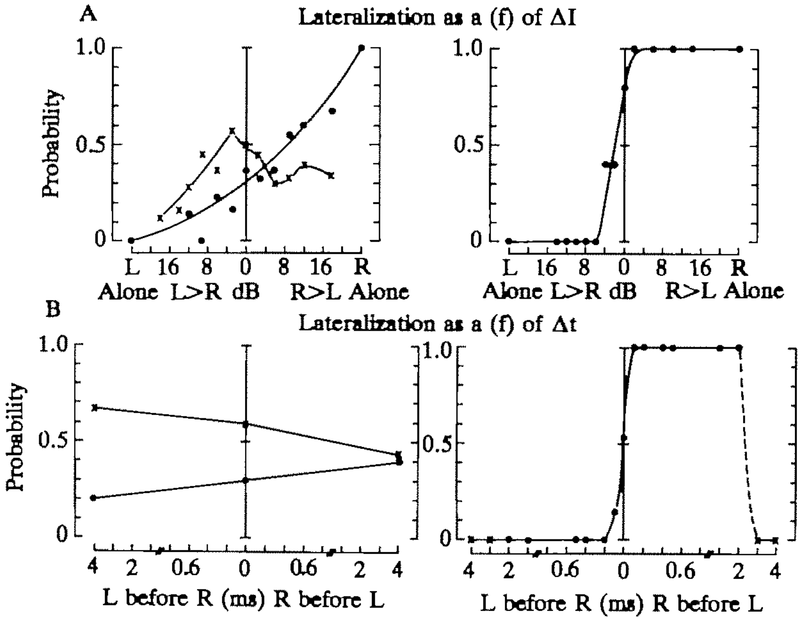

FIG. 5. Lateralization judgements (3/88) based on interaural intensity (A) and time (B) disparities in the patient (*left*) and her sister with normal hearing (*right*). Note the patient's failure to fuse the simultaneously presented binaural signals in A by the frequent report of 'two' clicks (x). For the patient, lateralization using interaural intensity differences was not complete even with a 36 dB difference in contrast to the 7 dB difference required for the sister The patient's failures of binaural fusion were not altered by introducing interaural time differences over an 8 ms range (B) The ordinate scale for B in the sister does not apply to the report as 'two' (x). With interaural time differences of greater than 2 ms the sister always reported hearing 2 clicks. Report as 'right' (●), report as 'two' (x)

stimuli was lost with interaural time differences of greater than 2 ms and 'two clicks' were reported. In contrast, the patient's probability of hearing either 'two clicks' or localizing a single click was not altered with changes in interaural timing disparities of up to 8 ms (fig. 5B).

Masking level difference

The patient showed no improvement of the masked threshold to a 300 Hz tone when the phase of the signal to one of the ears was reversed 180°. In contrast, the threshold of the normally hearing sister changed by 12 dB with the same procedure.

Binaural beats

The patient reported a 'wiggle' when a physical beat was presented monaurally. No beats were reported when the 2 tones were separated and presented binaurally. In contrast, both physical and binaural beats were discerned by the sister with normal hearing.

Monaural temporal resolution

A time separation of 90 – 100 ms between clicks was required by the patient to define the presence of 2 stimuli. In contrast, only a 2 – 4 ms separation was required by the sister with normal hearing for this same discrimination.

Somatosensory temporal resolution

A time separation of 40–50 ms was required by the patient to define the presence of paired stimuli to the median nerve at the wrist and 50–60 ms to the presence of paired stimuli on the skin of the middle finger. Comparable results for the sister were 40–50 ms for both types of stimuli.

Monaural signal duration

Both the patient and controls required comparable increments of duration of a tone burst to recognize it to be different from the 'standard' tone burst. For a 50 ms duration signal, the increment required was 20–30 ms for the patient similar to the mean of 20 ms for the controls; for the 500 ms duration tone the increment required was 200–300 ms, slightly in excess of the mean of 140 ms found in the controls.

Monaural gap detection

The length of the silent period within a tone burst that could be detected ranged between 15 and 20 ms for tones of 25–200 ms duration. When the duration of the tone was reduced below 25 ms, gap detection thresholds rose precipitously to 80 ms for signals of 10, 15 and 20 ms duration and, for signals of 5 ms duration, gap lengths as long as 200 ms could not be detected (fig. 6A). Normal subjects were able to detect silent periods of less than 2 ms for these same duration signals.

Monaural threshold as a function of tone duration

The threshold of a 1000 Hz tone rose 3 dB per halving of signal duration between 300 and 30 ms for both the patient and normals. For signal durations shorter than approximated 30 ms, thresholds for the patient abruptly increased to 20 dB for a halving of signal duration (fig. 6B).

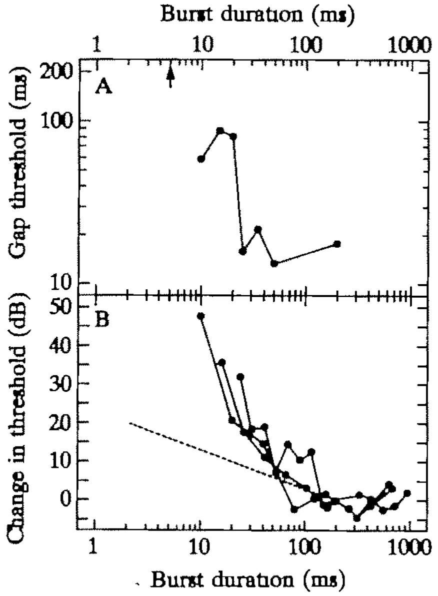

FIG. 6 A, the patient's monaural (right ear) threshold (tested 12/89) for detecting a silent period (gap detection) in a tone burst was approximately 15–20 ms for tones of 25–200 ms duration and increased abruptly to 60–80 ms with tones of 25 ms or less. With signal durations of 5 ms, gaps as long as 200 ms (the upper limit possible with the equipment) were not detectable as indicated by the arrow. B, monaural (right ear) threshold (tested 12/89) for a 1000 Hz tone as a function of signal duration is plotted in solid lines for the patient on 3 separate trials. Typical thresholds from normal subjects are represented by the dashed line. Note that the patients threshold/duration functions deviate from normal when tone duration is less than 40 ms

Frequency discrimination

The JNDs for pitch were elevated across all frequencies in the patient compared with the controls. The ratio of the absolute change in frequency in Hz divided by the frequency of the standard signal in Hz (DF/F) averaged for both ears showed the patient to require approximately a 3- to 15-fold increase compared with the controls.

Intensity discrimination

The JNDs for intensity were approximately twice those defined for the controls: 10 dB versus 4 dB, respectively. These values were the same at 200, 1000 and 4000 Hz.

DISCUSSION

In this study of a patient with a moderate-to-severe pure tone hearing loss, those auditory evoked potentials (brainstem, middle and long-latency) commonly used to assess the function of the cochlea and the central auditory pathways were absent. Other authors have reported occasional patients in whom auditory brainstem potentials were absent even though the stimuli were clearly suprathreshold (Worthington and Peters, 1980; Kraus *et al.*, 1984; C. Berlin, personal communication; J. Jerger, personal communication). The clinical details of both these patients and the present case are similar (Table 5). The patients first presented as children or young adults. Their audiological functions show a normal to moderate elevation of pure tone thresholds, absent middle ear reflexes, and impaired speech comprehension. Except for the absence or marked abnormality of the auditory brainstem potentials, the patients are neurologically normal. The constellation of these findings suggests a disorder of the eighth nerve and/or brainstem. These results also challenge our assumptions about the relationship between auditory function and evoked potentials.

Auditory brainstem potentials are used as an objective measure of the functioning of the cochlea and brainstem auditory pathway because their appearance correlates well with hearing threshold (Jerger and Mauldin, 1978; Pratt *et al.*, 1985; Kileny and Magathan, 1987). Our patient, and those reviewed above, are exceptions to this rule since they could 'hear' the click and tones employed without having evoked neural components of these traditional tests. In the present study, the failure to record these potentials was associated with an auditory perceptual deficit disproportionately affecting those perceptions dependent on temporal features of the acoustic signal. This finding bears on the suggestion by Worthington and Peters (1980) that 'the ABR is generated by only a portion of the auditory system'. The discussion will focus on the relationship between auditory evoked potentials and auditory perceptual capacities.

Evoked potentials

In this patient, a particular group of auditory evoked potentials was absent—auditory brainstem, middle and long-latency neural components—which reflects the responsiveness of the auditory system to 'transient' features of acoustic signals (Picton *et al.*, 1974). These tests were repeated three times over a 2-yr period and the absence of potentials is unlikely to be a technical error. The amplitude of the 'transient' type of evoked potential is directly related both to the rate at which signal intensity changes (rise and fall-times)

TABLE 5. AUDIOMETRIC TEST RESULTS (dB HL re ANSI) IN PATIENTS WITHOUT AUDITORY BRAINSTEM EVOKED POTENTIALS (RIGHT EAR/LEFT EAR)

	Case[1]	*Case*[2]	*Case*[3]	*Case*[4]	*Case*[5]
Age of onset (yrs)	7	17	2	5	18
Sex	F	M	M	F	M
Audiogram (Hz)					
250	35/50	65/55	25/15	15/55	NT/NT
500	40/55	70/45	10/10	60/35	25/25
1000	45/50	70/60	5/10	85/60	25/25
2000	35/25	65/65	5/5	80/55	25/25
4000	60/40	60/70	10/5	95/55	25/25
8000	50/65	65/65	15/5	90/NR	NR/NR
SRT (dB HL)	50/40	24/30	10/10	25/70	NT/NT
WDS (%)	36/0	0/0	80/80	2/3	65/65
Acoustic reflex	Absent/ Absent	Absent/ Absent	Absent/ Absent	Absent/ Absent	Absent/ Absent
Tympanometry	NT/ NT	Normal/ Normal	Normal/ Normal	Normal/ Normal	Normal/ Normal

SRT = speech reception thresholds, WDS = word intelligibility score; NT = not tested; NR = no response. [1] Test results obtained on 2/88 (Table 1) for our patient [2] A 19-yr-old male with severely reduced speech discrimination. No ABR found; a broad slow positive wave was noted between 250 and 300 ms post stimulus for both click and tone pips (Case 3, Worthington and Peters (1980) with additional information obtained from Dr Worthington). [3] A 6-yr-old male with language delays from age 2 yrs No ABR components were observed below 45 dB HL (Case 2, Worthington and Peters (1980) with additional information obtained from Dr Worthington) [4] A 14-yr-old female with a normal neurological examination and normal CT. No ABRs or middle-latency auditory evoked potentials (Case 4, Kraus *et al*, 1984). [5] A 20-yr-old male with difficulty understanding speech No ABRs found A normal slow vertex potential was defined (Case 2, Hildesheimer *et al.*, 1985).

and to the final intensity (Onishi and Davis, 1968; Hecox *et al.*, 1976; Salt and Thornton, 1984). These potentials are time-locked to the onset of the acoustic signal and, if the signal is sufficiently long, to its offset, but not to the steady unchanging portions of the signal (Onishi and Davis, 1968). It is important to recognize that these three evoked potentials are used in the clinical setting to assess both the peripheral and central portions of the auditory pathway without wide appreciation that they actually define the function of only a particular portion of the auditory system, that is, that dealing with responsiveness to rapid stimulus change. Moreover, in our patient the definition of normal amplitude cochlear microphonics when neural components of the evoked potentials, including wave I of the ABR, were absent, provide evidence that receptor hair cell function was most likely preserved, whereas neural activity beginning with the eighth nerve was impaired.

There are other auditory evoked potentials that are also sensitive to rapid stimulus change such as (1) the frequency following response (FFR) evoked by low-frequency signals consisting of components that reproduce the stimulus waveform (Moushegian *et al.*, 1973); and (2) the 40 Hz middle-latency potentials which have their dominant spectral energy at the stimulus repetition rate (Galambos *et al.*, 1981). The FFR was not present in our patient; however, it is often difficult to record in normal subjects (Moushegian *et al.*, 1973) and thus its absence cannot be used to help in the understanding of auditory function in this patient. The 40 Hz middle-latency response was not tested but the standard middle-latency components to 10/s stimulation were absent.

There is another type of auditory evoked potential recorded from the scalp that is sensitive to the unchanging aspects of an auditory stimulus. It is characterized by a sustained negative voltage shift which is maintained for the duration of the acoustic stimulus (Picton *et al.*, 1978). Such sustained potentials have also been recorded directly from the cortex of experimental animals (Gumnit, 1960) and probably represent maintained depolarization of neurons in auditory cortex. Recently, sustained magnetic fields accompanying steady-sound stimulation have been identified in humans as originating from temporal lobe (Hari *et al.*, 1987). The presence of sustained potentials in our patient provides objective evidence of the preservation of auditory cortical processes sensitive to maintained acoustic stimulation.

There are also components of auditory evoked potentials that reflect cognitive activities of the subject rather than sensory features of the stimulus and have thus been labelled 'cognitive' or 'endogenous' components (Hillyard *et al.*, 1978). The patient demonstrated several of these cognitive components while discriminating between two notes. These included a vertex positivity to the target stimuli occurring at a latency of approximately 500 ms, the P300 (Donchin, 1981), and a frontal negativity occurring during attention to the auditory signals (Näätänen, 1982). The amplitude of the P300 was comparable with normals but its latency in both the auditory and the visual target detection tasks was delayed. A P300 component was also elicited during the detection of an infrequent omission of regularly presented stimuli (Michalewski *et al.*, 1982) with a latency comparable with normals. These findings suggest some alterations in the speed of stimulus classification in the patient that are independent of stimulus modality. In keeping with this interpretation was the finding of slowed RTs in the patient compared with normals in both the visual and auditory target-detection tasks.

Auditory nontargets also elicited components (N160, P240) when sensory components of the long-latency evoked potentials collected when the patient was asleep were absent. The N160 and P240 components in the patient have features that are characteristic of endogenous or cognitive components rather than of exogenous or sensory components. First, the N160/P240 components fluctuated considerably in latency between averages even though the evoking stimuli were identical, whereas the N100/P200 components in normals are of relatively constant latency if the stimuli are of constant intensity (Michalewski *et al.*, 1986). Secondly, the N160/P240 are largest in the midline parietal region whereas the N100/P200 components are normally of largest amplitude centrally. Finally, the N160/P240 components were only present when the patient was awake and involved in a cognitive test. In contrast, in normals, the N100/P200 components are only slightly affected by state of arousal. Studies in normal subjects have suggested that cognitive or endogenous components of the auditory evoked potentials in normal subjects can appear as early as 130 ms (Ford and Hillyard, 1981) and peak at approximately 165 ms (Goodin *et al.*, 1978), values that are comparable with the latencies defined for the frontal negativity and the N165 in our patient.

The results of these evoked potential studies are compatible with the patient having a deficit in neural responsiveness to rapid temporal (transient) features of the acoustic stimulus, but preservation of responsiveness to other features such as maintained stimulation. Furthermore, during the performance of auditory discrimination tasks there is electrophysiological evidence of preserved cognitive processes dependent on cortical activity. The patient's deficit appears to involve neural elements in the peripheral portions of the auditory pathway, the eighth nerve, while sparing hair cells in the cochlea, and the cortical portions of the auditory pathway.

Auditory perceptual deficits

The patient was profoundly impaired in using temporal cues of the acoustic signal for perceptual judgements in contrast to those perceptions dependent on intensity or frequency information. Thus lateralization judgements using interaural time or intensity differences were absent or markedly impaired, whereas lateralization of binaural signals in patients with a cochlear type hearing loss is relatively unaffected (Häusler *et al.*, 1983). Lateralization abilities depend on binaurally sensitive neurons in the brainstem auditory pathway which are differentially responsive to stimuli as a function of the temporal relationship of neural inputs from the two sides (Galambos *et al.*, 1959; Goldberg and Brown, 1968). Interaural time differences are encoded by a delay in the neural input from one cochlea relative to the other. Interaural intensity differences for transient stimuli may be accompanied by differences in the latency of inputs to binaurally sensitive cells and can thus be considered as another example of a temporal code. We can use the binaural temporal code with precision, detecting interaural time differences of 10–20 μs and intensity differences of 0.5 dB by shifts in the intracranial localization of the image (Jeffress and McFadden, 1971). The patient's failure at integrating the temporal aspects of binaural signals was evident by her inability to form a single image on many of the trials and instead reporting that she heard 'two clicks'. She was also unable to hear binaural beats or to show a change in masked threshold of a low-frequency tone as a function of interaural differences in phase. Both these tasks also depend on the proper utilization of interaural differences in the timing of neural inputs (Wernick and Starr, 1968). In contrast, masking level difference effects on threshold have been reported as 'nearly normal' in patients with cochlear type hearing loss (Durlach *et al.*, 1981).

It is likely that the deficits in the use of binaural timing cues are secondary to a fundamental disorder of monaural encoding of temporal features of the acoustic stimulus. The patient required almost a 100 ms separation between monaurally presented paired clicks to distinguish that 2 stimuli were present. Normally, such a distinction is apparent with a time separation of approximately 2 ms (initially described by Exner (1875) and confirmed by Hirsh and Sherrick (1961)). The detection of a brief interruption of a tone or noise signal (gap detection) has also been used to measure temporal recovery functions of the auditory system (Plomp, 1964; Abel, 1972). The patient required almost a 10-fold increase in the silent period compared with normals with tones of moderate length (20 ms vs 2 ms). Gap detection thresholds increased to 80 ms when signal duration was reduced below 25 ms. The magnitude of the disordered gap detection in this patient far exceeds that encountered in patients with the usual cochlear type hearing loss (Tyler *et al.*, 1982). The marked impairment of monaural timing is consistent with our patient's poor speech and word comprehension that was disproportionate to the extent of her pure tone hearing loss. Phonemes comprise rapid changes of signal frequency that are characteristic for the junction between consonants and vowels (Umeda, 1975; Klatt, 1976). It is of interest that the patient had particular difficulty distinguishing words differing in their vowels and could more easily distinguish words based on their high-frequency consonants. The latter ability is usually severely impaired in patients with cochlear type hearing loss. An additional reflection of the patient's impaired processing of temporal features of acoustic signals was the steep rise in intensity needed for detection at threshold as the duration of the signal was shortened.

In contrast to the loss or marked impairment of auditory percepts dependent on temporal cues which were out of proportion to the changes in threshold, those percepts utilizing frequency or intensity features were less affected. The appreciation of an intensity difference between 2 tones required 5 dB more for the patient than for the controls. In contrast, patients with cochlear type hearing loss have an enhanced ability above normal to detect small increments in intensity, that is ≤1 dB (Jerger *et al.*, 1959; Turner *et al.*, 1989). Thus the evidence, with regard to intensity discrimination, is that our patient performed slightly poorer than normals and very differently from patients with a cochlear type hearing loss. With regard to frequency discrimination, the patient required approximately a 10-fold greater change of a test tone's frequency than did the controls to distinguish it from the 'standard' tone. The extent of this change is similar to that found in some patients with a cochlear type hearing loss (Tyler *et al.*, 1983).

Not all perceptions requiring the utilization of temporal cues were impaired. The patient demonstrated relatively normal temporal integration during the estimation of signal duration. Freyman and Nelson (1987) reported that in subjects with cochlear hearing loss, difference limens for duration were poorer (requiring greater stimulus duration increments) for long-duration tones than for short-duration tones as compared with a normal control group. To evaluate generalized rapid temporal processing in our patient we tested the somatosensory system in a manner similar to that used for the auditory system (distinguishing paired stimuli to the median nerve); the patient did not differ significantly from our control, indicating that the disorder of temporal processing was restricted to the auditory system. Tanaka *et al.* (1987) studied a patient with the syndrome of pure word deafness following bilateral lesions of the auditory cortex who had marked impairment in the use of temporal cues for auditory processing similar to our patient. However, in contrast to our results, Tanaka's patient also had a generalized defect in temporal resolving abilities, being deficient in the visual and somatosensory modalities as well.

Mechanisms

A disorder of the peripheral part of the auditory system at the cochlea and/or the eighth cranial nerve principally affecting the temporal precision of the neural coding and/or its transmission centrally could account for the loss of auditory percepts dependent on temporal cues and those evoked potentials sensitive to acoustic transients. There was much less of an effect on other auditory perceptual processes such as the distinction between the frequency of 2 tones, the intensity of 2 signals, and the duration of 2 signals. Moreover, those auditory evoked potentials not dependent on timing cues, such as the sustained negativity accompanying steady acoustic stimulation or those components associated with cognitive processing, were preserved. We propose that the site of the disorder is likely to be in the eighth nerve or at the synapse between the hair cell and eighth nerve since cochlear microphonics were present without accompanying signs of neural activity.

The synapse between hair cells and eighth nerve dendrites functions to preserve temporal cues of acoustic signals by its ability to regulate the timing of eighth nerve discharges precisely. Thus eighth nerve fibres discharge to low-frequency signals (e.g., up to 3000 Hz) during only one phase of the stimulus waveform and then only to a restricted portion of that wave (Rose *et al.*, 1967). Eighth nerve fibres arising from the basal or high-frequency portions of the basilar membrane sensitive to high frequencies, preserve temporal cues by their precise latency of discharge to the onset of transient stimuli (Kiang *et al.*, 1965).

A disorder of this synapse could affect the precision of eighth nerve fibre discharges. Myasthenia gravis provides an example of the effects of a synaptic disorder on temporal processes. In this disease, the postsynaptic membrane is abnormal due to the accumulation of antibodies at receptor sites (Lindstrom and Lambert, 1978). Normally, all the muscle fibres innervated by the same motor axon discharge within about 50 μs of one another (Stålberg *et al.*, 1971). In contrast, in myasthenic subjects, the discharge of individual muscle fibres innervated by the same axon are temporally dispersed, resulting in a time separation or 'jitter' of up to several hundred microseconds between similarly innervated muscle fibres (Stålberg *et al.*, 1976). A disorder of the synapse between hair cells and eighth nerve dendrites might result in an 'abnormal' temporal dispersion of the timing of eighth nerve discharges similar to that encountered in muscle fibres of myasthenics and thereby account for alterations of those percepts and evoked potentials dependent on temporal cues. Moreover, although the timing of discharge may be altered, transmission still occurs accounting, perhaps, for the relative preservation of information useful for other kinds of perception (i.e., pitch, intensity, duration). The locus of the synaptic disorder need not be at postsynaptic receptor sites, as in myasthenia gravis, but could be presynaptic affecting the release of transmitter and still account for alterations in the timing of eighth nerve fibre discharges.

An example of how temporal 'jitter' can affect evoked potentials was assessed using the cat's auditory brainstem potentials. We simulated 'jitter' in the timing of nerve impulses by introducing small shifts in the occurrence of the click stimuli relative to the averaging process. Usually click stimuli are presented at a fixed delay after the average is initiated to time-lock the evoked potentials to the averaging process. By introducing a variable delay of the click relative to the onset of averaging, the evoked potential components would have a changing temporal relation to the averaging process. In this example of 'jitter' (fig. 7), clicks were presented over a 1 ms period beginning 3 ms following the onset of the average. The brainstem components were effectively abolished whereas the slow potential on which the components arise was preserved, confirming that temporal 'jitter' effectively attenuates the amplitude of the fast neural components of this type of evoked potential. Since a slow potential was also not evident in the patient's ABR, the temporal dispersion may have been even more extensive resulting in the absence of even this slow wave. Alternatively the absence of the slow potential may be due to the high-pass recording filter being set at 100 Hz leading to the attenuation of this slow potential.

The proposed disorder of synaptic function may be related to the differentiation of the auditory periphery into two systems. The ganglion of the auditory nerve consists of two cell types: type I cells comprise 95% of the population and innervate inner hair cells; type II cells comprise 5% of the population and innervate outer hair cells (Spoendlin, 1969). The distribution of the dendrites of these two cell types within the cochlea differs such that several type I fibres make synaptic connections to a single inner hair cell whereas

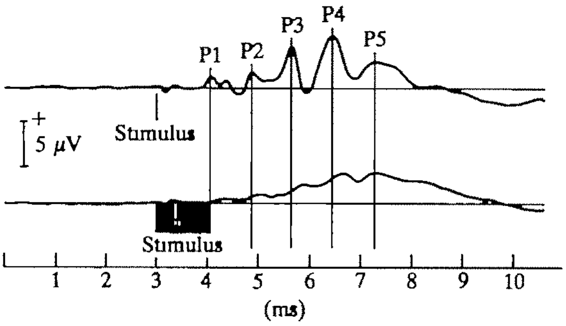

FIG 7 The effects of temporal 'jitter' on the amplitude of auditory brainstem potentials obtained from a cat In the top average all the stimuli were presented 3 ms after the onset of the average. In the bottom average the clicks were evenly dispersed over a 1 ms interval, beginning 3 ms after the start of the average. Note the marked attenuation of the components of the ABR accompanying the 'jitter' with the preservation of the slow potential shift. The components are labelled by their polarity at the vertex electrode (P for positive) and their approximate latency in ms. The recordings were made between the vertex referenced to the frontal sinus.

a single type II fibre makes synaptic connection to many outer hair cells (Brown, 1987). The physiological significance of this difference is not known. However, as Lim and coworkers (Lim, 1969; Lim and Anniko, 1985) have suggested, this arrangement could allow for differences in the encoding of auditory cues. Type I fibres are well situated for the preservation of timing cues with several different type I fibres making synaptic connection to just one inner hair cell, thus favouring a relative synchrony of discharge amongst those neurons. In contrast, each type II neuron establishes connections to many outer hair cells which differ from the outer hair cells receiving connections to other type II neurons. The separate connectivities of type II neurons make temporal synchrony between type II cells unlikely. Unfortunately, only a little is known about the functional differences between these two cell types (Patuzzi and Robertson, 1988). The finding of normal cochlear microphonics in our patient is evidence that the outer hair cells are probably preserved since they are the presumed principal generators of this receptor potential. The status of the inner hair cells and the type I fibres cannot be directly assessed. It is the loss of both temporally dependent auditory perceptions and neural components of auditory evoked potentials sensitive to temporal cues that suggests to us that the patient may have a defect of inner hair cell-type I/eighth nerve system as the basis for the auditory impairments.

Generalizations derived from a single case study must be viewed cautiously. However, the results from this patient provide new insights into the auditory and neural bases of auditory evoked potentials by emphasizing the importance of timing information for the generation of certain evoked potentials. The relevance of temporal cues for both evoked potentials and temporal integration has also been noted in patients with multiple sclerosis in whom abnormalities of particular components of the auditory brainstem potentials are accompanied by alterations in lateralization judgements dependent on binaural timing cues (Van der Poel *et al.*, 1988). The mechanism we have suggested to account for the patient's deficits, for example, a disorder of the precision of temporal encoding in the eighth nerve, may also be relevant for understanding other types of 'central' hearing impairment. There is relatively little information available regarding pitch, loudness and temporal auditory processing in patients with disorders of hearing. The results from the patient of this report suggest that these percepts may be differentially affected. The quantification of temporal, frequency and loudness perceptual abilities may be important to classify further and to understand some of the mechanisms underlying the different types of hearing disorders.

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REFERENCES

ABEL SM (1972) Discrimination of temporal gaps. *Journal of the Acoustical Society of America*, **52**, 519–524.

BERNARD PA, SOULIER MJ (1983) Abnormal brainstem response audiometry in normal patients. *Journal of Otolaryngology*, **12**, 194–196.

BROWN MC (1987) Morphology of labeled afferent fibers in the guinea pig cochlea. *Journal of Comparative Neurology*, **260**, 591–604.

BUCHWALD JS, HUANG C-M (1975) Far-field acoustic response: origins in the cat. *Science*, **189**, 382–384.

CACACE AT, SATYA-MURTI S, GRIMES CT (1983) Frequency selectivity and temporal processing in Friedreich's ataxia: clinical aspects in two patients. *Annals of Otology, Rhinology and Laryngology*, **92**, 276–280.

COATS AC, DICKEY JR (1970) Nonsurgical recording of human auditory nerve action potentials and cochlear microphonics. *Annals of Otology, Rhinology and Laryngology*, **79**, 844–852.

DONCHIN E (1981) Surprise! . . . Surprise? *Psychophysiology*, **18**, 493–513.

DURLACH NIH, THOMPSON CL, COLBURN HS (1981) Binaural interaction in impaired listeners: a review of past research. *Audiology*, **20**, 181–211.

EXNER S (1875) Experimentelle Untersuchung der einfachsten psychischen Processe. *Pflügers Archiv für die Gesamte Physiologie*, **11**, 403–432.

FORD JM, HILLYARD SA (1981) Event-related potentials (ERPs) to interruptions of a steady rhythm. *Psychophysiology*, **18**, 322–330.

FREYMAN RL, NELSON DA (1987) Frequency discrimination of short- versus long-duration tones by normal and hearing-impaired listeners. *Journal of Speech and Hearing Research*, **30**, 28–36.

GALAMBOS R, SCHWARTZKOPFF J, RUPERT A (1959) Microelectrode study of superior olivary nuclei. *American Journal of Physiology*, **197**, 527–536.

GALAMBOS R, DESPLAND P-A (1980) The auditory brainstem response (ABR) evaluates risk factors for hearing loss in the newborn. *Pediatric Research*, **14**, 159–163.

GALAMBOS R, MAKEIG S, TALMACHOFF PJ (1981) A 40-Hz auditory potential recorded from the human scalp. *Proceedings of the National Academy of Sciences of the USA*, **78**, 2643–2647.

GOLDBERG JM, BROWN PB (1968) Functional organization of the dog superior olivary complex: an anatomical and electrophysiological study. *Journal of Neurophysiology*, **31**, 639–656.

GOODIN DS, SQUIRES KC, HENDERSON BH, STARR A (1978) An early event-related cortical potential. *Psychophysiology*, **15**, 360–365.

GUMNIT RJ (1960) D.C. potential changes from auditory cortex of cat. *Journal of Neurophysiology*, **23**, 667–675.

HARI R, PELIZZONE M, MÄKELÄ JP, HÄLLSTRÖM J, LEINONEN L, LOUNASMAA OV (1987) Neuromagnetic responses of the human auditory cortex to on- and offsets of noise bursts. *Audiology*, **26**, 31–43.

HÄUSLER R, COLBURN S, MARR E (1983) Sound localization in subjects with impaired hearing: spatial-discrimination and interaural-discrimination tests. *Acta Oto-laryngologica*, Supplement 400.

HECOX K, GALAMBOS R (1974) Brain stem auditory evoked responses in human infants and adults. *Archives of Otolaryngology*, **99**, 30–33.

HECOX K, SQUIRES N, GALAMBOS R (1976) Brainstem auditory evoked responses in man. I. Effect of stimulus rise-fall time and duration. *Journal of the Acoustical Society of America*, **60**, 1187–1192.

HILDESHEIMER M, MUCHNIK C, RUBINSTEIN M (1985) Problems in interpretation of brainstem-evoked response audiometry results. *Audiology*, **24**, 374–379.

HILLYARD SA, PICTON TW, REGAN D (1978) Sensation, perception and attention: analysis using ERPs. In: *Event-Related Brain Potentials in Man*. Edited by R. Callaway, P. Tueting and S. H. Koslow. New York and London: Academic Press, pp. 223–321.

HIRSH IJ, SHERRICK CE (1961) Perceived order in different sense modalities. *Journal of Experimental Psychology*, **62**, 423–432.

JABBARI B, SCHWARTZ DM, MACNEIL DM, COKER SB (1983) Early abnormalities of brainstem auditory evoked potentials in Friedreich's ataxia: evidence of primary brainstem dysfunction. *Neurology, Cleveland*, **33**, 1071–1074.

JEFFRESS LA, MCFADDEN D (1971) Differences of interaural phase and level in detection and lateralization. *Journal of the Acoustical Society of America*, **49**, 1169–1179.

JERGER J, SHEDD JL, HARFORD E (1959) On the detection of extremely small changes in sound intensity. *Archives of Otolaryngology*, **69**, 200–211.

JERGER J, MAULDIN L (1978) Prediction of sensorineural hearing level from the brain stem evoked response. *Archives of Otolaryngology*, **104**, 456–461.

KIANG N, WATANABE T, THOMAS E, CLARK F (1965) Discharge patterns of single fibers in the cat's auditory nerve. *Research Monograph*. Cambridge: MIT Press.

KILENY PR, MAGATHAN MG (1987) Predictive value of ABR in infants and children with moderate to profound hearing impairment. *Ear and Hearing*, **8**, 217–221.

KLATT DH (1976) Linguistic uses of a segmental duration in English: acoustic and perceptual evidence. *Journal of the Acoustical Society of America*, **59**, 1208–1221.

KRAUS N, ÖZDAMAR Ö, STEIN L, REED N (1984) Absent auditory brain stem response: peripheral hearing loss or brain stem dysfunction? *Laryngoscope*, **94**, 400–406.

LIM DJ (1969) Three dimensional observation of the inner ear with the scanning electron microscope. *Acta Oto-laryngologica*, Supplement 255.

LIM DJ, ANNIKO M (1985) Development morphology of the mouse inner ear: scanning electron microscopic observation. *Acta Oto-laryngologica*, Supplement 422.

LINDSTROM JM, LAMBERT EH (1978) Content of acetylcholine receptor and antibodies bound to receptor in myasthenia gravis, experimental autoimmune myasthenia gravis, and Eaton-Lambert syndrome. *Neurology, Minneapolis*, **28**, 130–138.

MICHALEWSKI HJ, PATTERSON JV, BOWMAN TE, LITZLEMAN DK, THOMPSON LW (1982) A comparison of the emitted late positive potential in older and young adults. *Journal of Gerontology*, **37**, 52–58.

MICHALEWSKI HJ, PRASHER DK, STARR A (1986) Latency variability and temporal interrelationships of the auditory event-related potentials (N1, P2, N3, and P3) in normal subjects. *Electroencephalography and Clinical Neurophysiology*, **65**, 59–71.

MØLLER AR, JANNETTA P, BENNETT M, MØLLER MB (1981) Intracranially recorded responses from the human auditory nerve: new insights into the origin of brain stem evoked potentials (BEPs). *Electroencephalography and Clinical Neurophysiology*, **52**, 18–27.

MOUSHEGIAN G, RUPERT AL, STILLMAN RD (1973) Scalp-recorded early responses in man to frequencies in the speech range. *Electroencephalography and Clinical Neurophysiology*, **35**, 665–667.

NÄÄTÄNEN R (1982) Processing negativity: an evoked-potential reflection of selective attention. *Psychological Bulletin*, **92**, 605–640.

ONISHI S, DAVIS H (1968) Effects of duration and rise time of tone bursts on evoked *V* potentials. *Journal of the Acoustical Society of America*, **44**, 582–591.

PATUZZI R, ROBERTSON D (1988) Tuning in the mammalian cochlea. *Physiological Reviews*, **68**, 1009–1082.

PICTON TW, HILLYARD SA, KRAUSZ HI, GALAMBOS R (1974) Human auditory evoked potentials. I: Evaluation of components. *Electroencephalography and Clinical Neurophysiology*, **36**, 179–190.

PICTON TW, WOODS DL, PROULX GB (1978) Human auditory sustained potentials. I. The nature of the response. *Electroencephalography and Clinical Neurophysiology*, **45**, 186–197.

PLOMP R (1964) The ear as a frequency analyzer. *Journal of the Acoustical Society of America*, **36**, 1628–1636.

Pratt H, Shenhav R, Goldsher M (1985) Applications of auditory evoked potentials to evaluate hearing disorders: assets and limitations. *Israel Journal of Medical Sciences*, **21,** 44–49.

Rose JE, Brugge JF, Anderson DJ, Hind JE (1967) Phase-locked response to low-frequency tones in single auditory nerve fibers of the squirrel monkey. *Journal of Neurophysiology*, **30,** 769–793.

Salt AN, Thornton ARD (1984) The effects of stimulus rise-time and polarity on the auditory brainstem responses. *Scandinavian Audiology*, **13,** 119–127.

Satya-Murti S, Wolpaw JR, Cacace AT, Schaffer CA (1983) Late auditory evoked potentials can occur without brainstem potentials. *Electroencephalography and Clinical Neurophysiology*, **56,** 304–308.

Spoendlin H (1969) Innervation patterns in the organ of Corti of the cat. *Acta Oto-laryngologica*, **67,** 239–254.

Stålberg E, Ekstedt J, Broman A (1971) The electromyographic jitter in normal human muscles. *Electroencephalography and Clinical Neurophysiology*, **31,** 429–438.

Stålberg E, Trontelj JV, Schwartz MS (1976) Single-muscle-fiber recording of the jitter phenomenon in patients with myasthenia gravis and in members of their families. *Annals of the New York Academy of Sciences*, **274,** 189–202.

Starr A (1986) Auditory brainstem potentials: their theory and practice in evaluating neural function. In: *A Textbook of Clinical Neurophysiology*. Edited by A. M. Halliday, S. R. Butler and R. Paul. Chichester and New York: John Wiley, pp. 383–389.

Starr A, Achor LJ (1975) Auditory brainstem responses in neurological disease. *Archives of Neurology, Chicago*, **32,** 761–768.

Starr A, Hamilton AE (1976) Correlation between confirmed sites of neurological lesions and abnormalities of far-field auditory brainstem responses. *Electroencephalography and Clinical Neurophysiology*, **41,** 595–608.

Tanaka Y, Yamadori A, Mori E (1987) Pure word deafness following bilateral lesions: a psychophysical analysis. *Brain*, **110,** 381–403.

Turner CW, Zwislocki JJ, Filion PR (1989) Intensity discrimination determined with two paradigms in normal and hearing-impaired subjects. *Journal of the Acoustical Society of America*, **86,** 109–115.

Tyler RS, Summerfield Q, Wood EJ, Fernandes MA (1982) Psychoacoustic and phonetic temporal processing in normal and hearing-impaired listeners. *Journal of the Acoustical Society of America*, **72,** 740–752.

Tyler RS, Wood EJ, Fernandes M (1983) Frequency resolution and discrimination of constant and dynamic tones in normal and hearing-impaired listeners. *Journal of the Acoustical Society of America*, **74,** 1190–1199.

Umeda N (1975) Vowel duration in American English. *Journal of the Acoustical Society of America*, **58,** 434–445.

Van der Poel JC, Jones SJ, Miller DH (1988) Sound lateralization, brainstem auditory evoked potentials and magnetic resonance imaging in multiple sclerosis. *Brain*, **111,** 1453–1474.

Wernick JS, Starr A (1968) Binaural interaction in the superior olivary complex of the cat: an analysis of field potentials evoked by binaural-beat stimuli. *Journal of Neurophysiology*, **31,** 428–441.

Worthington DW, Peters JF (1980) Quantifiable hearing and no ABR: paradox or error? *Ear and Hearing*, **1,** 281–285.

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ADDENDUM

Acoustic emissions were recorded from a microphone in the right ear canal to click stimuli at intensities as low as 58 dB SPL. The patient's perceptual threshold for these same click stimuli required intensities of at least 80 dB SPL. The left ear could not be tested because of the presence of a ventilation tube in the tympanic membrane. This finding supports the interpretation that the outer hair cells are preserved in this patient.

REFERENCE

Lutman ME, Mason SM, Sheppard S, Gibbin KP (1989) Differential diagnostic potential of otoacoustic emissions: a case study. *Audiology*, **28,** 205–210.

Brain (1991), **114**, 1181–1196

HERPES ZOSTER MYELITIS

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SUMMARY

We studied the clinical (10 patients) and pathological (9 patients) findings in 13 patients with herpes zoster myelitis, all of whom had systemic illnesses associated with immunosuppression. The median interval between the onset of the herpes zoster rash and myelopathic symptoms was 12 days, and the subsequent median interval to maximal deficit was 10.5 days. Presenting neurological symptoms were characteristically ipsilateral to the rash, with motor dysfunction predominating, followed by a spinothalamic and, less often, posterior column sensory deficit. Pathological involvement was most severe in the dorsal root entry zone and posterior horn of the spinal cord segment corresponding to the involved dermatome. There was variable spread both horizontally and vertically in the spinal cord. Direct varicella-zoster virus (VZV) infection of neuroectodermal cells, particularly oligodendrocytes, was demonstrated by immunostaining viral antigens (8 cases), and by the presence of Cowdry type A intranuclear inclusions (7 cases) and often was associated with focal demyelination (6 cases). In 4 patients a VZV vasculitis was associated with leptomeningitis and haemorrhagic necrosis (spinal cord in 1; brainstem or cerebellum in 3). The protracted evolution in many cases and the pathologically documented direct viral infection of the spinal cord provide a rational basis for the use of antiviral therapy in preventing or attenuating the evolving myelopathy.

INTRODUCTION

Herpes zoster (HZ; shingles) is a sporadic illness caused by varicella-zoster virus (VZV) and is characterized by a vesicular dermatomal rash. It results from reactivation of latent infection of sensory ganglion neurons established years earlier during the course of primary infection, that is, chickenpox (varicella) (Hope-Simpson, 1965). Although HZ is characteristically benign, neurological complications are nonetheless common and range from transient pain and paraesthesiae associated with the acute rash to postherpetic neuralgia (Hope-Simpson, 1975; Portenoy *et al.*, 1986), segmental sensory loss or motor paresis (Kendall, 1957; Thomas and Howard, 1972), encephalitis (Jemsek *et al.*, 1983), myelitis (Hardy, 1876), and cerebral vascular occlusion (MacKenzie *et al.*, 1981; Eidelberg *et al.*, 1986).

Clinical myelopathy is a rare complication of HZ that usually develops in the immunocompromised host. In large series, the incidence varies from 0 to 0.8% in the general population or in immunosuppressed patients, respectively (Schimpff *et al.*, 1972; Mazur and Dolin, 1978; Ragozzino *et al.*,1982). Although HZ myelitis was first reported by Hardy in 1876, most subsequent reports have described only single or a

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few cases (Bruce, 1907; Lhermitte and Nicolas, 1924; Thalhimer, 1924; Bellavitis, 1931; Biggart and Fisher, 1938; Wilson, 1940; Denny-Brown *et al.*, 1944; Kendall, 1957; Boudin *et al.*, 1958; McAlpine *et al.*, 1959; Harrison, 1964; Rose *et al.*, 1964; Force *et al.*, 1968; McCormick *et al.*, 1969; Nyberg-Hansen, 1972; Hogan and Krigman, 1973; Richmond, 1974; Sachdeva *et al.*, 1975; Gardner-Thorpe *et al.*, 1976; Rao and Ramanamurty, 1976; Cole, 1978; Ruppenthal, 1980; Corston *et al.*, 1981; Cullis *et al.*, 1982; Muder *et al.*, 1983; Mas and Lapresle, 1985; Yeolekar *et al.*, 1985).

We reviewed our own experience with 13 patients and additionally analysed the 33 previously reported cases in order to define more clearly the clinical features, pathological characteristics and pathogenesis of this disorder.

MATERIAL AND METHODS

On review of the clinical and pathological records of patients at the Memorial Sloan-Kettering Cancer Center and the New York Hospital from 1970 to 1986 we identified 13 with a diagnosis of HZ myelitis. The diagnosis was based on clinical grounds: (1) characteristic rash; (2) spinal cord dysfunction; (3) exclusion of alternative causes of myelopathy (e.g., tumour, multiple sclerosis) by clinical and laboratory findings; and (4) absent or only mild supraspinal central nervous system (CNS) signs and symptoms at presentation. The diagnosis of HZ myelitis was based solely on clinical diagnosis in 4 patients, on pathological diagnosis in 2 patients, and on both clinical and pathological diagnoses in the remaining 7 patients.

In 9 patients with complete postmortem examination, brains and spinal cords were fixed in 10% formalin for 2 wks, cut into 1 cm or 0.5 cm serial sections; representative sections were embedded in paraffin. The microscopic sections were stained with haematoxylin and eosin, luxol fast blue-haematoxylin and eosin, and Bodian's silver stain. A high-titre herpes zoster convalescent human serum was used as the primary antibody (Horten *et al.*, 1981; Eidelberg *et al.*, 1986) to detect the presence of VZV antigen by the avidin biotin complex (ABC) immunoperoxidase technique using commercially obtained secondary antibody and ABC complex (Vector Laboratories Inc., Burlingame, CA). Paraffin-embedded brain from a known case of VZV encephalitis was used as a positive control. On selected blocks, immunostaining was performed for herpes simplex virus types 1 and 2, and cytomegalovirus with commercially available antibodies (Ortho Laboratories, Bridgewater, NJ).

Inclusion of previously reported cases was based on less restrictive criteria: the presence of a characteristic rash and either the development of myelopathy in temporal relation to the rash or pathological findings that excluded other causes and were consistent with herpes zoster myelitis. Twenty-seven cases with clinical evidence of HZ myelitis were identified among the 33 literature cases. The clinical findings in the previously reported cases are described along with our own findings in the results section, while the less complete pathological findings described in the literature are presented in the Discussion.

RESULTS

Our own series included 8 men and 5 women with a mean age of 49 yrs (median 44, range 19–86 yrs). All had predisposing disease which included Hodgkin's disease (3 patients), non-Hodgkin's lymphoma (2 patients), acute lymphocytic leukaemia (1 patient), the acquired immune deficiency syndrome (AIDS) (3 patients), metastatic carcinoma (3 patients) and renal failure (1 patient). The initial zoster rash was right-sided in 5 patients, left-sided in 6, bilateral in 1 and either absent or unnoticed in 1 autopsied case; dissemination of the rash occurred in 5 patients. The dermatonal distribution of the rash was cervical in 1 patient, thoracic in 9 patients, and lumbosacral in 3 patients.

The literature series included 13 men, 15 women, and 5 not classified with regard to sex. The mean age was 55 yrs (median 59, range, 16–81 yrs). An underlying illness was reported in 7 of 33 patients: neurosyphilis and rheumatoid arthritis each in 2 patients, and lymphoma, ovarian carcinoma, and congestive heart failure each in 1 patient. The initial zoster rash was right-sided in 19 patients, left-sided in 10, and bilateral in 1; dissemination of the rash was not reported. The dermatomal distribution was trigeminal in 1 patient, cervical in 6, thoracic in 21, and lumbosacral in 1.

Clinical presentation

Symptoms and signs of spinal cord dysfunction usually began within 3 wks of the onset of the rash (fig. 1A). Among our 9 patients with adequate documentation, myelopathic manifestations developed 5–21 days after the initial rash (median, 12 days). Among documented literature cases (n = 22), onset of spinal cord dysfunction developed from 8 days before to 10 wks after initial rash (median, 14 days).

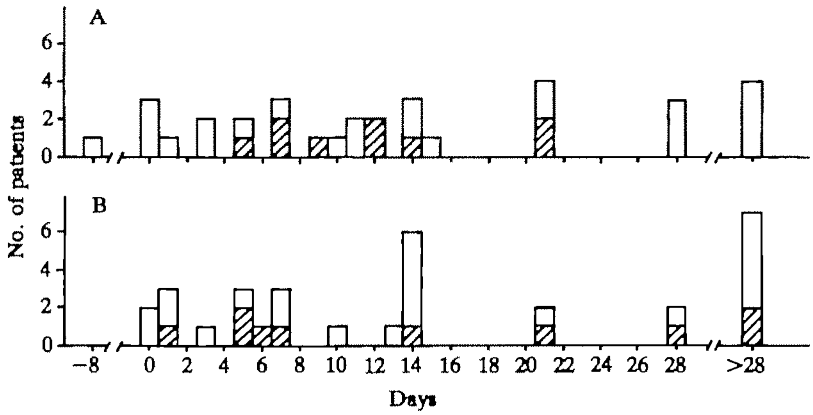

FIG. 1 Timing of myelopathy in relation to the onset of herpes zoster rash. A, interval between the rash and onset of myelopathic symptoms. B, interval between the onset of myelopathic symptoms and maximal neurological deficit. Hatched bars = authors' series; open bars = literature series

Subacute progression occurred in most patients (fig. 1B). In our own series, maximal deficit usually occurred within 3 wks of initial myelopathy (median, 10.5 days); exceptions included 2 AIDS patients with long intervals (2 and 6 mos) separating the initial and maximal neurological deficit. Among literature cases, maximal neurological deficit occurred within 10 wks (median, 14 days).

Leg weakness and sensory abnormalities were the most common presenting symptoms in the 38 patients from the combined series in whom clinical information was available (Table 1). Lower limits weakness occurred in 74% of these patients and was usually unilateral. Sensory abnormalities were present in 53% of all patients. A Brown-Séquard syndrome was noted in 4 patients and bladder dysfunction in 7.

The most advanced neurological deficit included lower limb weakness in 35 patients in whom information was available, with paraparesis in 80%. Sensory loss occurred in 26 of the 35 (74%) patients and included a sensory level to all modalities in 12 (34%) patients. Pain and temperature sensation was impaired more often than vibration and

TABLE 1 NEUROLOGICAL MANIFESTATIONS OF HERPES ZOSTER MYELITIS

Neurological manifestation	*No. of patients*					
	At presentation			*Maximal*		
	MSKCC/NYH and literature combined			*MSKCC/NYH and literature combined*		
	(n = 11)	*(n = 27)*	*(n = 38)*	*(n = 11)*	*(n = 24)*	*(n = 35)*
Weakness						
Unilateral leg	6	9	15	3	4	7
Paraparesis/plegia	2	6	8	7	12	19
Triparesis (1 arm)	0	3	3	0	3	3
Quadriparesis	0	0	0	0	3	3
Hemiparesis	1	1	2	1	2	3
Total	9	19	28	11	24	35
Sensory loss						
Pain/temperature						
Unilateral	0	4	4	0	3	3
Bilateral	2	1	3	7	12	19
Vibration/position						
Unilateral	0	2	2	0	1	2
Bilateral	2	1	3	5	8	13
Dysaesthesia-paraesthesiae-numbness						
Unilateral	3	4	7	0	1	1
Bilateral	2	6	6	0	3	3
Spinal level to all modalities	0	1	1	4	9	12
Total*	7	13	20	7	19	26
Pain	1	5	6	1	4	5
Brown-Séquard syndrome	1	3	4	0	3	3
Sphincter disturbance						
Bladder	1	6	7	3	14	17
Bowel	0	3	3	1	5	6

* Patients often had multiple abnormalities

position sense (63% vs 43%). Sphincter disturbances involved the bladder in 17 patients and bowel in 6 patients.

Laboratory tests were more useful in excluding other causes of myelopathy than in specifically identifying VZV. Myelography was normal in all 9 of our own and 6 of the literature patients in which it was performed. Lumbar cerebrospinal fluid (CSF) pressure was usually normal or slightly elevated. CSF pleocytosis was found in 20 of 27 patients in the combined series. Monocytes and lymphocytes usually comprised more than 90% of the white blood cells (WBCs), although polymorphonuclear leucocytes comprised 5–40% in 6 patients and were more frequent in patients with rapid onset and severe disease. Erythrocytes were present in the CSF of 5 patients; in 3 of these, there were between 150 and 1100 red cells/mm^3. The CSF protein concentration was > 2.5 mmol/l in 15 of 22 patients. In general, the greatest CSF pleocytosis and protein elevation occurred near the time of maximal deficit. CSF glucose was normal (> 2.5 mmol/l) in 15 of 16 patients. The patient with an abnormally low value (1.9 mmol/l) had 1760 WBC/mm^3 (40% polymorphonuclear leucocytes) in the CSF and extensive necrosis pathologically (fig. 2, Case 2). Bacterial, viral and fungal culture and cytology were negative in all cases in which they were obtained. Specific VZV cultures were not obtained.

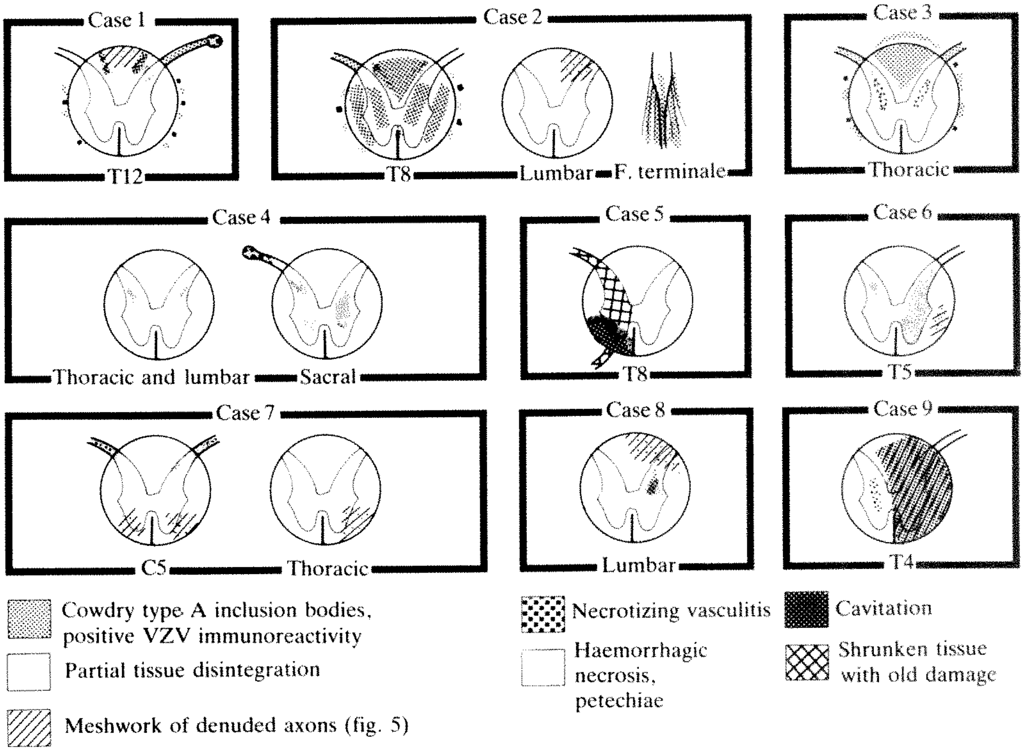
Case 1
T12
Case 2
T8
Lumbar
F. terminale
Case 3
Thoracic
Case 4
Thoracic and lumbar
Sacral
Case 5
T8
Case 6
T5
Case 7
C5
Thoracic
Case 8
Lumbar
Case 9
T4
Cowdry type A inclusion bodies, positive VZV immunoreactivity
Partial tissue disintegration
Meshwork of denuded axons (fig. 5)
Necrotizing vasculitis
Haemorrhagic necrosis, petechiae
Cavitation
Shrunken tissue with old damage

FIG. 2. Summary of pathological findings of herpes zoster myelitis of 9 cases of the present study.

Twelve patients were treated for herpes zoster myelitis and received glucocorticoids and/or antiviral agents (vidarabine or acyclovir). Eight received glucocorticoids alone: 3 improved, 3 deteriorated, and 2 showed no change. Two of the 3 patients who improved during steroid treatment were unusual cases from the literature who exhibited a relapsing course and in whom neuropathological examination was not performed (McAlpine *et al.*, 1959; Nyberg-Hanson, 1972).

Vidarabine monotherapy was associated with clinical improvement in both patients treated, including 1 who had deteriorated during a previous trial of glucocorticoids. In another patient vidarabine was used with glucocorticoids and the progressive disease stabilized. Acyclovir monotherapy was used in 1 non-AIDS patient who improved, and in 2 AIDS patients. One of the latter improved during treatment but deteriorated several weeks later. The other was begun on treatment 2 wks after the onset of neurological symptoms because of delay in seeking medical attention, and showed no apparent response.

Information on neurological outcome, based on follow-up examination 1–24 mos after maximal neurological illness, was available in 25 patients: recovery was complete in 3 and partial in 16, while 6 had little or no improvements. Those who improved appreciably were generally patients with a milder deficit; of the 3 patients with 'complete' recovery, none had paraplegia or a dense sensory level, and sphincter disorder had been absent (2 patients) or mild (1 patient with urinary frequency). Improvement in the 16 patients with partial recovery included motor, sensory and sphincter function without apparent preference. At least 3 patients with paraparesis became ambulatory. Persistent pain was described in 2 patients. Neurological improvement was not clearly related to the location of the rash, the time period from the rash to initial CNS disease or from initial to maximal neurological deficit, or involvement of specific spinal cord pathways (e.g., motor or sensory). Patients in whom the neurological deficit was static for at least 2 days were unlikely to progress further. Recovery usually commenced within 2 wks of maximal deficit, and the greatest improvement occurred during the subsequent 2 mos, although some continued to improve after 1 yr.

Sixteen of 45 patients in the combined series (11 of our 13 patients) died within 4 mos of initial rash. The HZ myelitis and its secondary complications (e.g., pulmonary embolism and decubitus ulcers causing sepsis) contributed to the death of 14 patients. Follow-up information was available for 14 patients with immunosuppressive disorders; 11 died within 4 mos of rash and only 3 showed partial recovery.

Neuropathology

Pathological findings in our 9 patients with postmorten examination are summarized in Table 2 and fig. 2. The most severely affected spinal cord levels were within two segments of the initial rash in all 6 patients for whom information was available. Pathological changes were limited to one region of the spinal cord in 6 patients and were multiple in 3 (Cases 2, 4, 7). Six of the 9 patients had bilateral lesions and in 2 of these (Cases 2, 9) single level lesions involved nearly the entire transverse section.

Dorsal root ganglia supplying the initially involved dermatomes were available in only 2 cases. They showed extensive haemorrhagic necrosis associated with necrotizing vasculitis and thrombosis. Cowdry type A intranuclear inclusions were seen in a majority of the ganglion and satellite cells, and were also observed in many endothelial and adventitial cells.

Eight of the 9 patients had abnormalities in the posterior nerve roots. These included mild lymphocytic infiltration (2 patients), focal areas of pallor (2 patients), axonal spheroids (1 patient), and haemorrhagic necrosis with acute inflammation (2 patients). In all 4 of the cases tested, VZV immunoreactivity was present and in 3, Cowdry type A intranuclear inclusion bodies were found in epineural fibroblasts and cells within the endoneurium, the morphology of which was consistent with their being Schwann cells. One patient (Case 9), who survived 6 mos after clinical myelopathy, had atrophic and fibrotic posterior nerve roots.

The posterior horns were abnormal in all 9 cases and in 6 of the 9 cases there was bilateral involvement. Pathological changes included focal or diffuse necrosis (5 patients), mild inflammation (2 patients), and only mild changes of capillary proliferation and

TABLE 2 SUMMARY OF CLINICOPATHOLOGICAL FINDINGS

Case and diagnosis	*Age (yrs) sex*	*Clinical level*	*Duration from neurological symptoms to death*	*Maximal neurological deficit*	*VZV CNS lesion*
1 Hodgkin's disease	19 M	R T12 Disseminated	1 day	Confusion, R LE; weakness	Focal necrosis (medulla, pons MB, CBL)
2 Breast carcinoma	61 F	L T10 Disseminated	3 days (11 days)	Flaccid paraplegia, extensor plantars, T7 sensor level for PS and TS, T9 sensory level for VS, TPS	Focal necrosis (medulla), ependymitis (4th)
3 Hodgkin's disease	25 M	L T8–9 Disseminated	1 wk	Lethargic, L hemiparesis (4/5), extensor plantars, L UE dysmetria, decreased sensation to all modalities (no clear level)	Focal necrosis (medulla, pons)
4 Hodgkin's disease	74 F	L L3 Disseminated	4 wks	Stupor, meningism, bilateral extensor plantars	Focal necrosis, vasculitis (medulla, 4th vent.)
5. Lymphoma	53 M	L T8	4 mos	L Horner's syndrome, L LE spastic weakness; (4/5), L extensor plantar, T8 sensory level to PS and TS; minimal distal VS loss, NL JPS	–
6. Renal failure	81 F	R T4–5	?	—	—
7 Lymphoma	44 M	C5–6	?	–	Perivascular lymphocytes (medulla)
8. Oat cell carcinoma of lung	67 F	–	?	–	Meningeal vasculitis (brainstem)
9. AIDS	36 M	–	6 mos	Flaccid paraplegia; no report of sensory exam	–

R = right; L = left; UE = upper extremity, LE = lower extremity; CSF = cerebrospinal fluid, NL = normal, C = cervical; T = thoracic, L = lumbar, VS = vibration sense; JPS = joint position sense, PS = pain sensation, TS = temperature sensation; MB = midbrain, CBL = cerebellum.

parenchymal rarefaction (2 patients) (fig. 3). Inclusion bodies were present in 5 patients. The posterior horn in 1 patient (Case 5) was atrophic and gliotic.

Wedge-shaped regions of demyelination were present in 6 of the 9 patients. These were located near the root entry zone corresponding to the clinically involved dermatomes (fig. 4A, B). Axons were relatively well preserved although occasionally swollen and beaded (fig. 5). Scattered lipid-laden macrophages and scanty fibrillary astrocytes were seen within the demyelinated regions. Oligodendrocytes were markedly decreased.

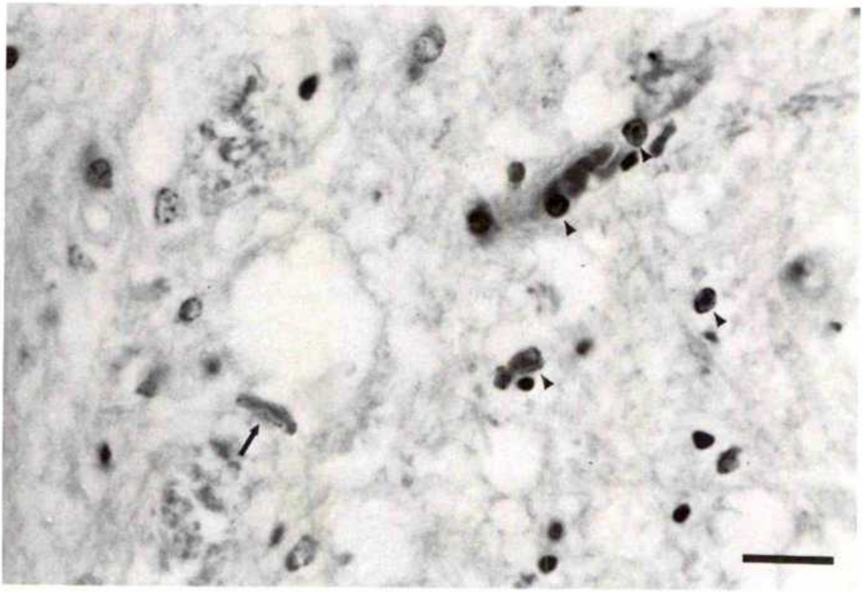

FIG. 3. Posterior horn with multiple intranuclear inclusion bodies of Cowdry type A in oligodendrocytes (arrow head) and a probable neuron (arrow). Note disintegrating neuropil with oedema. (*Case 8*). Hematoxylin-eosin. Bar = 100 μm.

Intranuclear Cowdry type A inclusion bodies and cytoplasmic VZV immunoreactivity were seen in occasional macrophages and astrocytes within and adjacent to the demyelinated lesions (fig. 6). Wallerian degeneration was not observed.

Two patients had extensive transverse involvement of thoracic spinal cord at approximately one level. In 1 (Case 9), a large region of recent demyelination with sheets of lipid-laden macrophages and preserved axons involved more than half of a transverse section of thoracic spinal cord (fig. 7A, B). A focal area of chronic demyelination was present in the posterior columns within this lesion. The second patient (Case 2) had necrotizing transverse myelitis with vasculitis at this thoracic level and a small area of demyelination at a lumbar level. In both patients, these areas contained abundant inclusion bodies and VZV reactivity.

Three of 9 patients did not have demyelination in the spinal cord. One (Case 3) had numerous inclusion bodies and VZV positivity in the posterior columns with little evidence of tissue disruption. The second (Case 5) showed cavitation near an anterior root entry zone with a narrow rim of partial necrosis in which inclusion bodies and VZV reactivity were detected. The third (Case 4) had no white matter lesions.

Acute necrotizing vasculitis, found in 4 patients, was present around the involved segments of the spinal cord and brainstem in 3 patients and found only in the medulla in the fourth. The vasculitis was associated with haemorrhagic necrosis in 2 of the 3 patients with brainstem vasculitis and in 1 patient with spinal cord vasculitis. However, in 1 patient (Case 2) with complete transverse myelitis there was acute haemorrhagic necrosis, involving the entire cross-section of the spinal cord, accompanied by numerous

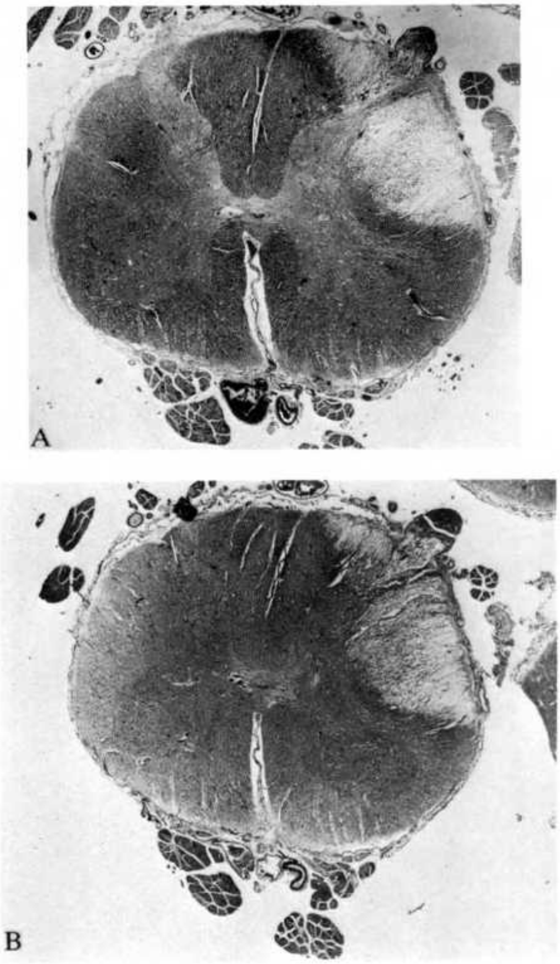

FIG. 4. Large wedge-shaped lesion involving both posterior and lateral columns including the posterior root entry zone. A, total absence of myelin on Luxol fast blue staining. B, preserved meshwork of demyelinated axons on Bodian's silver stain. (*Case 8*, thoracic spinal cord).

inclusion bodies and cytoplasmic VZV immunoreactivity in adventitial and endothelial cells of the involved vessels and in adjacent leptomeningeal arachnoid cells.

Four patients had an associated focal VZV encephalitis characterized by necrosis and demyelination associated with inclusion bodies and VZV immunoreactive cells. The involved regions included the nuclei gracilis and cuneatus in 3 patients (fig. 8), fourth ventricular ependyma in 2 patients, upper brainstem in 2 patients, and cerebellar cortex in 1 patient. Although all 4 patients with VZV encephalitis had leptomeningeal or parenchymal vasculitis, only a few foci were haemorrhagic and appeared to be related to vasculitis.

Additional neuropathological changes included vascular myelopathy (Petito *et al.*,

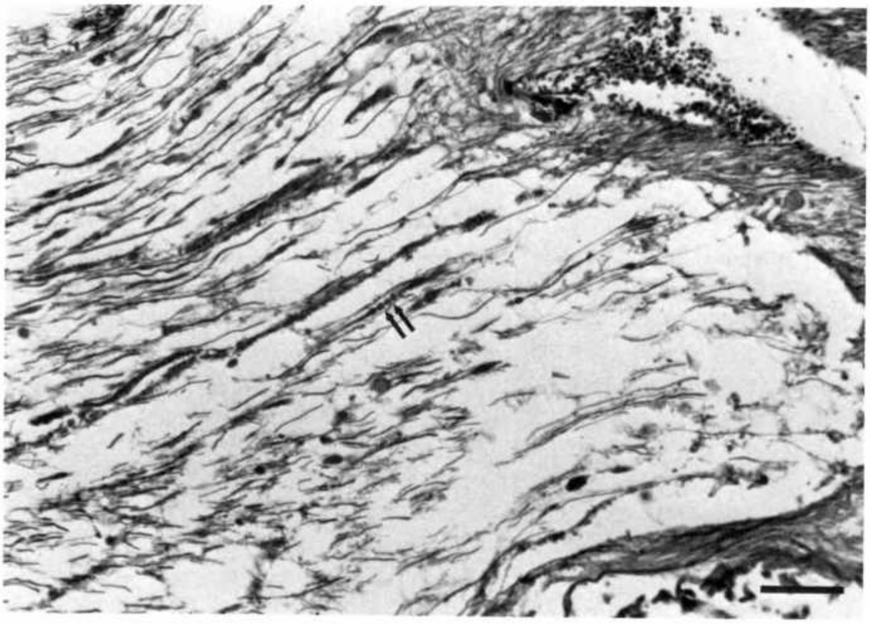

FIG. 5. Higher magnification of demyelinated meshwork, illustrated in fig. 4, with relatively well preserved axons. Note beaded appearance in some axons (arrows). (*Case 8*). Bodian's silver impregnation. Bar = 100 μm.

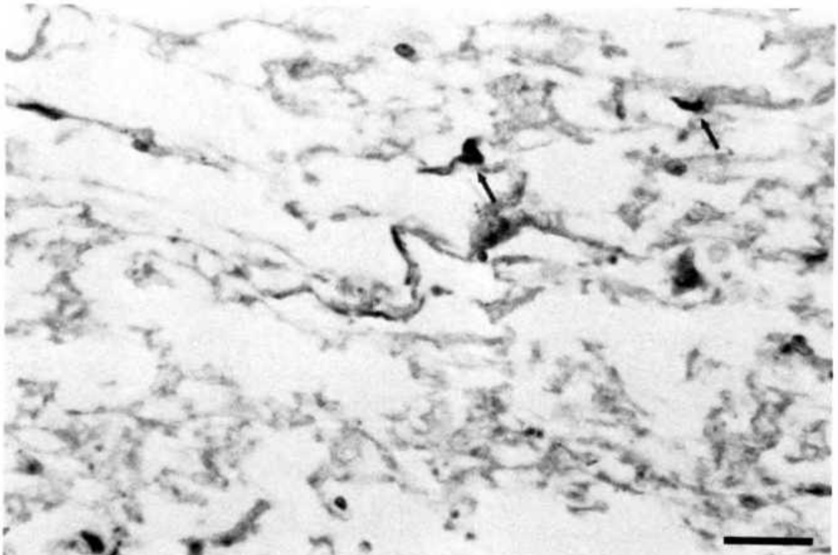

FIG. 6. Higher magnification of demyelinated meshwork, illustrated in fig. 4, with immunocytochemical staining of VZV antigen in a few astrocytes (arrow). Note total absence of oligodendrocytic nuclei in the field. (*Case 8*). Bar = 100 μm.

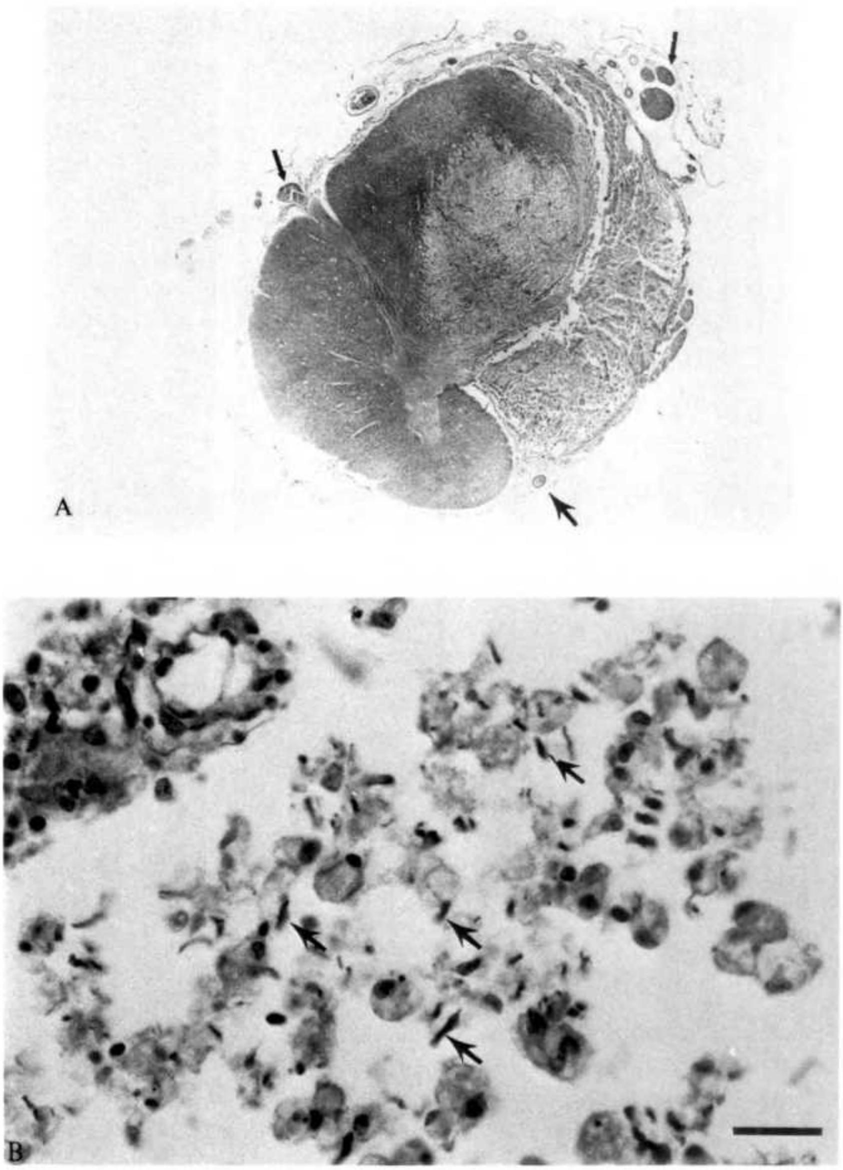

FIG. 7. A, large area of demyelination with ongoing organization involving entire anterior and lateral columns, and more than a half of the posterior column. The affected half is shrunken, disfiguring the shape of the spinal cord. (*Case 9*, thoracic spinal cord, anterior sulcus (large arrow), posterior roots (small arrows)). B, higher magnification of the demyelinating lesion illustrated in A. Note numerous lipid-laden macrophages and axons with cigar-butt appearance (arrow) in this transverse section. (*Case 9*, thoracic spinal cord). Bodian's silver impregnation. Bar = 100 μm.

1985) in 3 patients (Cases 5, 8, 9), multinucleated-cell encephalitis related to HIV infection in 1 patient (Case 9), and a lacunar infarct in 1 patient (Case 5).

There was a good correlation between clinical and pathological findings with regard

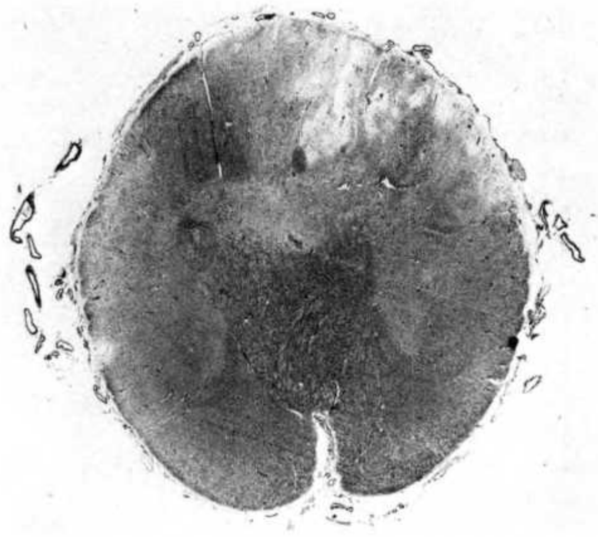

FIG. 8. A large area of tissue destruction, necrotic and demyelinating, involving the gracile and cuneate nuclei. (*Case 3*, medulla). Luxol fast blue.

to initial dermatomal rash and maximal spinal cord pathology, paraplegia/complete sensory level and transverse necrosis. Clinicopathological correlation was variable in patients with focal demyelination in lateral and posterior columns.

DISCUSSION

Herpes zoster myelitis produces a characteristic clinical profile. Onset is usually subacute with a mean delay of 2 wks between the initial rash and the neurological disturbance. One patient developed myelopathy before the rash, but had experienced dermatomal pain 8 days before myelopathy. In 8 patients, myelopathic symptoms were delayed 4 or more wks after the rash began. The temporal course was variable with the disease evolving over 1 – 3 wks, although in some patients the deficit was maximal within hours or days.

Neurological symptoms usually began unilaterally or, if bilateral, were asymmetric, with principal involvement of motor and posterior column functions altered ipsilateral to the rash, and spinothalamic sensory functions altered contralaterally. The constellation of symptoms and signs varied, but motor manifestations usually predominated followed by spinothalamic and posterior column sensory abnormalities. In occasional patients, bladder dysfunction or central pain (i.e., from spinal cord involvement) was a presenting feature. Maximal neurological deficit included weakness in all patients (Table 1), with over two-thirds evolving to paraplegia or paraparesis. Sensory findings were also very frequent, with pain and temporary sensory loss more common than vibratory and proprioceptive sensory loss. A spinal level to all modalities occurred in more than one-third of patients. Sphincter disturbances were present in almost half of the patients.

The diagnosis of HZ myelitis was usually not difficult when neurological symptoms developed in temporal proximity to the rash, although in some patients, encephalopathy obscured signs and symptoms of myelopathy. Initial differential diagnoses include acute transverse myelitis of unknown cause (Altrocchi, 1963), spinal cord compression from mass lesions, and inflammatory polyneuropathy. Characteristically, patients present with pain and rash but do not have prominent back pain preceding or at the time of myelopathy. In patients with lymphoma or other metastatic tumours, differentiation must be made between cases in which herpes zoster is 'triggered' by local epidural disease which may subsequently evolve to compress the spinal cord (Head and Campbell, 1900). In such complex cases, myelography or spinal magnetic resonance imaging, along with CSF analysis, are indicated to clarify the diagnosis.

While the CSF profile usually includes a mononuclear pleocytosis with normal or elevated protein, inflammatory cells may be absent or minimal, or conversely, may include many polymorphonuclear leucocytes. Although findings are usually more severe than in segmental zoster without myelopathy, they can overlap with those of uncomplicated HZ. CSF anti-VZV antibody production may indicate direct CNS infection (Jemsek *et al.*, 1983), but this may not be helpful in the presence of necrosis or inflammation with blood-brain barrier disruption.

The major neuropathological findings in this study include posterior horn abnormalities in all 9 patients, demyelination in 6/9 patients, and vasculitis with necrosis in 4/9 patients. Previous neuropathological reports of HZ myelitis found necrotizing inflammatory myelopathy with or without associated vasculitis (Lhermitte and Nicolas, 1924; Bellavitis, 1931; Denny-Brown *et al.*, 1944; Boudin *et al.*, 1958; Rose *et al.*, 1964; Hogan and Krigman, 1973; Ruppenthal, 1980). Although demyelination has been reported previously, it has not been described as a prominent pathological feature (Rose *et al.*, 1964; Hogan and Krigman, 1973; Ruppenthal, 1980; Cullis *et al.*, 1982). The demyelination may be secondary to viral infection and destruction of oligodendrocytes since Cowdry type A inclusions were usually seen in cells resembling oligodendrocytes. In contrast, transverse myelitis, seen in 2 patients, was accompanied by cord necrosis most probably resulting from direct VZV cord infection and possibly immune-mediated demyelination. In the patient with transverse myelitis and VZV vasculitis, cord ischaemia probably contributed to cord necrosis.

Pathological involvement of the spinal cord conformed to the clinical localization, with the most severe or predominant pathology developing at the same segment of the spinal cord as the involved dorsal root ganglion.

The spinal cord pathology in our series suggest four principal mechanisms of injury: (1) direct infection and/or immune-mediated destruction of oligodendrocytes with resultant demyelination; (2) infarction secondary to vasculitis; (3) leptomeningitis; and (4) infection of other components including neurons, astrocytes and ependymal cells. Spread of the virus into the spinal cord was demonstrated in all our cases by presence of typical Cowdry type A inclusion bodies or by immunohistochemical detection of VZV antigens.

The location and type of the pathological changes allow a hypothetical reconstruction of the usual pathogenic events involved in the development of myelopathy. The virus usually spreads peripherally by axoplasmic transport and presumably exploits those mechanisms that are involved in directing normal macromolecular traffic towards the periphery (Price, 1986). Our study suggests that central spread of virus from dorsal root ganglia to cord causes myelitis since most of our cases had intranuclear inclusion bodies in Schwann cells and fibroblasts of posterior roots. The prolonged interval between peripheral spread (shingles) and central spread (myelopathy), however, suggests that cell-to-cell contact, rather than intraaxonal spread, may be the major route of central passage. This type of spread may be more readily interrupted by immune defences in the normal host but may proceed in patients with compromised cell-mediated immunity. Subsequent viral spread within the cord apparently can occur concentrically within the cord, both laterally and vertically. Once extending beyond the grey matter, infection appears to preferentially involve oligodendrocytes, leading to demyelination, which was prominent in 6 of our cases and is similar to that accompanying VZV encephalitis in immunosuppressed patients (Horten *et al.*, 1981; Morgello *et al.*, 1988). The presence of intranuclear inclusions and VZV antigens in the gracile and cuneate nuclei in 4 of our cases without infection of intervening spinal cord suggests that axoplasmic transport of VZV within the spinal cord also occurs. Three of these 4 patients also had focal areas of viral infection in the posterior columns.

This study suggests that early therapeutic intervention is beneficial. The characteristic delayed development and slow evolution of HZ myelitis in most patients, in concert with the efficacy of newer antiviral drugs, particularly acyclovir (Shepp *et al.*, 1986), suggest that these drugs can prevent multiplication and spread of the virus in the CNS. The therapeutic efficacy of antiviral agents could not be assessed because of limited data in our series. However, it is reasonable to suggest that patients with HZ myelitis be treated promptly with intravenous acyclovir. The pathological finding of active viral infection as the basis of cord injury clearly supports this contention. In contrast, the role of corticosteroids in the treatment of the myelopathy is less clear. While secondary immunopathological processes may contribute to the pathology, it is likely that they are less important than direct viral infection and that the immunosuppressive effects of corticosteroids can blunt host defences which clear the virus. In certain cases it may be worthwhile to explore the use of corticosteroids under antiviral 'coverage'.

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REFERENCES

Altrocchi PH (1963) Acute transverse myelopathy. *Transactions of the American Neurological Association*, **88,** 186–188.

Bellavitis C (1931) Nevrassite da herpes-zoster: contributo clinica-anatomico. *Revista di Neurologia*, **4,** 337–362.

Biggart JH, Fisher JA (1938) Meningo-encephalitis complicating herpes zoster. *Lancet*, **ii,** 944–946.

Boudin G, Barbizet J, Brion S, Pépin B (1958) L'encéphalo-myélite zostérienne: à propos de deux observations anatomo-cliniques. *Revue Neurologique*, **99,** 535–557.

Bruce A (1907) Unusual sequela of herpes zoster (? posterior poliomyelitis). *Review of Neurology and Psychiatry*, **5,** 885–896.

Cole M (1978) Myelopathy associated with herpes zoster. *Rocky Mountain Medical Journal*, **75,** 317–319.

Corston RN, Logsdail S, Godwin-Austen RB (1981) Herpes-zoster myelitis treated successfully with vidarabine. *British Medical Journal*, **283,** 698–699.

Cullis PA, Gilroy J, Cushing R (1982) Herpes zoster myelitis treated with vadarabine. *Journal of Neurology, Neurosurgery and Psychiatry*, **45**, 94.

Denny-Brown D, Adams RD, Fitzgerald PJ (1944) Pathologic features of herpes zoster: a note on 'geniculate herpes'. *Archives of Neurology and Psychiatry, Chicago*, **51**, 216–231.

Eidelberg D, Sotrel A, Horoupian DS, Neumann PE, Pumarola-Sune T, Price RW (1986) Thrombotic cerebral vasculopathy associated with herpes zoster. *Annals of Neurology*, **19**, 7–14.

Force L, Jouffe G Martin, Perrouty P (1968) Deux paralysies zostériennes: zona thoracique sui vi de myélite et paralysie vélo-laryngée au cours d'un zona géniculé. *Marseille Medical*, **105**, 381–383.

Gardner-Thorpe C, Foster JB, Barwick DD (1976) Unusual manifestation of herpes zoster: a clinical and electrophysiological study. *Journal of the Neurological Sciences*, **28**, 427–447.

Hardy M (1876) Du zona. *Gazette des Hôpitaux Civils et Militaires*, **49**, 827–828.

Harrison RJ (1964) Zoster myelitis presenting with acute retention of urine. *Proceedings of the Royal Society of Medicine*, **57**, 589–590.

Head H, Campbell AW (1900) The pathology of herpes zoster and its bearing on sensory localisation. *Brain*, **23**, 353–523.

Hogan EL, Krigman MR (1973) Herpes zoster myelitis: evidence for viral invasion of spinal cord. *Archives of Neurology, Chicago*, **29**, 309–313.

Hope-Simpson RE (1965) The nature of herpes zoster: a long-term study and a new hypothesis. *Proceedings of the Royal Society of Medicine*, **58**, 9–20.

Hope-Simpson RE (1975) Postherpetic neuralgia. *Journal of the Royal College of General Practitioners*, **25**, 571–575.

Horten B, Price RW, Jimenez D (1981) Multifocal varicella-zoster virus leukoencephalitis temporally remote from herpes zoster. *Annals of Neurology*, **9**, 251–266.

Jemsek J, Greenberg SB, Taber L, Harvey D, Gershon A, Couch RB (1983) Herpes zoster-associated encephalitis: clinicopathologic report of 12 cases and review of the literature. *Medicine, Baltimore*, **62**, 81–97.

Kendall D (1957) Motor complications of herpes zoster. *British Medical Journal*, **ii**, 616–618.

Lhermitte J, Nicolas M (1924) Les lésions spinales du zona. La myélite zostérienne. *Revue Neurologique*, **1**, 361–364.

McAlpine D, Kuroiwa Y, Toyokura Y, Araki S (1959) Acute demyelinating disease complicating herpes zoster. *Journal of Neurology, Neurosurgery and Psychiatry*, **22**, 120–123.

McCormick WF, Rodnitzky RL, Schochet SS, McKee AP (1969) Varicella-zoster encephalomyelitis: a morphologic and virologic study. *Archives of Neurology, Chicago*, **21**, 559–570.

MacKenzie RA, Forbes GS, Karnes WE (1981) Angiographic findings in herpes zoster arteritis. *Annals of Neurology*, **10**, 458–464.

Mas JL, Lapresle J (1985) Myélite zostérienne: étude immunologique et traitement par l'acyclovir. *Revue Neurologique*, **141**, 234–236.

Mazur MH, Dolin R (1978) Herpes zoster at the NIH: a 20 year experience. *American Journal of Medicine*, **65**, 738–744.

Morgello S, Block GA, Price RW, Petito CK (1988) Varicella-zoster virus leukoencephalitis and cerebral vasculopathy. *Archives of Pathology and Laboratory Medicine*, **112**, 173–177.

Muder RR, Lumish RM, Corsello GR (1983) Myelopathy after herpes zoster. *Archives of Neurology, Chicago*, **40**, 445–446.

Nyberg-Hansen R (1972) Relapsing herpes zoster myelitis. *Acta Neurologica Scandinavica*, **48**, Supplement 51, 397–400.

Petito CK, Navia BA, Cho E-S, Jordan BD, George DC, Price RW (1985) Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *New England Journal of Medicine*, **312**, 874–879.

Portenoy RK, Duma C, Foley KM (1986) Acute herpetic and postherpetic neuralgia: clinical review and current management. *Annals of Neurology*, **20**, 651–664.

Price RW (1986) Neurobiology of human herpesvirus infections. *CRC Critical Reviews in Clinical Neurobiology*, **2**, 61–123.

Ragozzino MW, Melton LJ, Kurland LT, Chu CP, Perry HO (1982) Population-based study of herpes zoster and its sequelae. *Medicine, Baltimore*, **61**, 310–316.

Rao KS, Ramanamurty DV (1976) Herpes zoster – transverse myelitis. *Journal of the Indian Medical Association*, **66**, 41–42.

RICHMOND W (1974) The genito-urinary manifestations of herpes zoster: three case reports and a review of the literature. *British Journal of Urology*, **46**, 193–200.

ROSE FC, BRETT EM, BURSTON J (1964) Zoster encephalomyelitis. *Archives of Neurology, Chicago*, **11**, 155–172.

RUPPENTHAL M (1980) Changes of the central nervous system in herpes zoster. *Acta Neuropathologica, Berlin*, **52**, 59–68.

SACHDEVA JR, BEHAL RA, SINGH J (1975) Zoster myelitis (a case report). *Journal of the Association of Physicians of India*, **23**, 783–784.

SCHIMPFF S, SERPICK A, STOLER B, RUMACK B, MELLIN H, JOSEPH JM *et al.* (1972) Varicella-zoster infection in patients with cancer. *Annals of Internal Medicine*, **76**, 241–254.

SHEPP DH, DANDLIKER PS, MEYERS JD (1986) Treatment of varicella-zoster virus infection in severely immunocompromised patients: a randomized comparison of acyclovir and vidarabine. *New England Journal of Medicine*, **314**, 208–212.

THALHIMER W (1924) Herpes zoster; central nervous system lesions similar to those of epidemic (lethargic) encephalitis: report of a case. *Archives of Neurology and Psychiatry, Chicago*, **12**, 73–79.

THOMAS JE, HOWARD FM (1972) Segmental zoster paresis—a disease profile. *Neurology, Minneapolis*, **22**, 459–466.

WILSON SAK (1940) *Neurology*. Baltimore: Williams and Wilkins, p. 675.

YEOLEKAR ME, BANAVALI S, MENON PS (1985) Pre-eruption herpes zoster myelitis. *Journal of the Association of Physicians of India*, **33**, 185.

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WORD DEAFNESS AND AUDITORY CORTICAL FUNCTION

A CASE HISTORY AND HYPOTHESIS

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SUMMARY

A patient who already had Wernicke's aphasia due to a left temporal lobe lesion suffered a severe deterioration specifically of auditory language comprehension, subsequent to right temporal lobe infarction. A detailed comparison of his new condition with his language status before the second stroke revealed that the newly acquired deficit was limited to tasks related to auditory input. Further investigations demonstrated a speech perceptual disorder, which we analysed as due to deficits both at the level of general auditory processes and at the level of phonetic analysis. We discuss some arguments related to hemisphere specialization of phonetic processing and to the disconnection explanation of word deafness that support the hypothesis of word deafness being generally caused by mixed deficits.

INTRODUCTION

Pure word deafness, or auditory verbal agnosia, is a rare disorder of auditory language comprehension. It is characterized by a selective impairment of auditory verbal comprehension with preservation of other language functions. However, both the selectivity for verbal material and the preservation of other language functions are matters of dispute (Goldstein, 1974; Buchman *et al.*, 1986). Given the rare occurrence of pure cases, Buchman *et al.* dropped the adjective 'pure' and adopted 'word deafness' to designate 'a disparity between auditory verbal comprehension and other linguistic functions'. Thus defined, it still remains a distinctive syndrome which has drawn the attention of many neurologists and neuropsychologists.

Opinions diverge as to the functional locus of the auditory verbal recognition disorder in word deafness. Agnosias were originally conceived of as central recognition disturbances, although a distinction between apperceptive and associative types was made in its history by Lissauer (1890) and later by others (Geschwind, 1965; Vignolo, 1969; Bauer and Rubens, 1985). In the last two decades attempts to characterize impairments in individual patients have focused on speech perceptual deficits. Most authors have emphasized impairments of low level general auditory processes (Jerger *et al.*, 1969; Albert and Bear, 1974; Chocholle *et al.*, 1975; Auerbach *et al.*, 1982; Miceli, 1982;

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Coslett *et al.*, 1984; Motomura *et al.*, 1986; Tanaka *et al.*, 1987; Yaqub *et al.*, 1988; Buchtel and Stewart, 1989). In contrast, Saffran *et al.* (1976), Caramazza *et al.* (1983) and Metz-Lutz and Dahl (1984) implicated phonetic processes, that is, a stage of auditory processing specific to speech.

In theories of speech perception, the distinction between phonetic and auditory processes indicates that some aspects of speech perception are specifically linguistic (phonetic processes), while others are not (general auditory processes) (Liberman *et al.*, 1967; Repp, 1982; Kuhl, 1986; Pisoni and Luce, 1987). Clearly, the extraction of phonetic structure from the physical speech signal requires the operation of basic processes that register, for example, intensity, frequency, and duration. But how these general auditory processes relate to specialized phonetic processes is unresolved. It is, for instance, not known what kind of auditory processes are crucial for the perception of speech. What is known, though, is that phonetic analysis is probably a left hemisphere-based competence (Studdert-Kennedy and Shankweiler, 1970; Studdert-Kennedy *et al.*, 1972; Tartter, 1988). Hence left hemisphere lesions, especially of the auditory cortex, might have a disruptive effect on speech perception. This expectation is, however, only partially met. Recent studies have confirmed that phonetic analysis may be deficient in aphasia, but these phonetic impairments are not strongly correlated with auditory language comprehension impairments (for a review, *see* Blumstein, 1987). Also, studies comparing left and right hemisphere-damaged patients have not contributed much to the identification of the auditory processes underlying speech perception (*see*, e.g., Divenyi and Robinson, 1989). Given these unresolved questions it is surprising that so many authors of recent case reports have assumed deficits of general auditory processes as the cause of word deafness (Albert and Bear, 1974; Auerbach *et al.*, 1982; Miceli, 1982; Coslett *et al.*, 1984; Tanaka *et al.*, 1987; Yaqub *et al.*, 1988; Buchtel and Stewart, 1989).

We report a case of word deafness, which was studied using neurolinguistic and speech perception investigations similar to those used by earlier authors. These investigations helped to delimit the nature of the patient's disturbance and to generate hypotheses regarding the contribution of auditory and phonetic deficits. In the case we studied, an unusual circumstance provided an additional source of evidence bearing on the role of auditory versus phonetic deficits. As a Wernicke's aphasic, the patient had already participated in various neurolinguistic experiments when he sustained a second cerebral infarct, which was located temporoparietally in the right hemisphere and made him word deaf. This sequence of events provided the opportunity to repeat earlier tests and to perform new experiments in order to chart in detail the differences between the old and the new patterns of deficits. The newly acquired deficit appeared to be limited to a disorder of speech perception and was difficult to reduce to either an acoustic or a phonetic type of deficit (Auerbach *et al.*, 1982).

CASE DESCRIPTION

The patient is a 57-yr-old right-handed man. He was first admitted in December 1984, when he had suddenly experienced difficulties in speaking. His past medical history included myocardial infarct at age 44, from which he fully recovered. He is university educated and held a position as professor. His native language is Dutch. General physical examination was unremarkable. Neurological examination revealed mild right-sided facial weakness. There was no visual field loss on confrontation. A very slight right hemiparesis and mild right hyperreflexia were noticed. The right plantar response was extensor. There was no hemi-inattention or apraxia. A cerebral CT scan (fig. 1) demonstrated a left middle cerebral artery infarction. Left carotid angiography was normal. Electrocardiography showed signs of old anteroseptal infarction. Echocardiography revealed no evidence for a cardiac source of emboli.

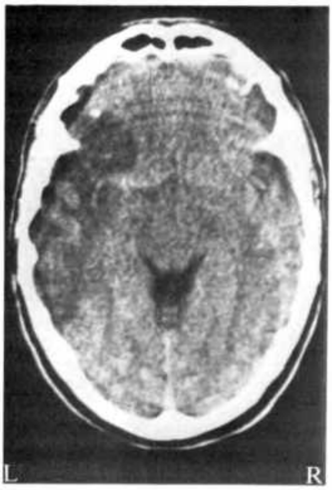

FIG. 1. Unenhanced CT scan performed on admission after first stroke.

The patient had fluent speech, mainly consisting of jargon and empty phrases. Repetition was severely disturbed, although individual sounds could be repeated to some extent. Auditory and written language comprehension were both affected. He was tested formally using the Dutch version of the Aachen Aphasia Test (AAT) (Huber *et al.*, 1984) and classified as a severe Wernicke's aphasic. As such he participated in a number of neurolinguistic experiments. In the course of 16 months he improved to the extent that retesting with the ATT demonstrated a shift, on all subtests, from severely disturbed to a disturbance of average degree.

In January 1988 the patient consulted his neurologist because of a hearing disturbance, which had been preceded by mild complaints of headache and nausea. On admission he reported that sounds seemed louder and noisy. It had occurred to him that he did not recognize the sound of an airplane passing and that music sounded strange. Before the onset of this disturbance he often played the piano, but he had recently stopped. His speech seemed unchanged, but he did not understand any spoken language. The interview with the patient as well as his communication with relatives and nurses proceeded with written messages.

General physical examination revealed normal heart rate, rhythm, and blood pressure. There were no bruits. Neurological examination showed no abnormalities of cranial nerve function, no visual field defect, and normal motor and sensory functions. The tendon reflexes were symmetric, but the left plantar response was extensor.

A CT scan revealed a hypodense area in the distribution of the right middle cerebral artery having the appearance of a fresh ischaemic infarct. Digital subtraction angiography of the extracranial cerebral vessels showed no abnormalities. There was right temporoparietal theta activity in an EEG. Electrocardiography and echocardiography contributed no new information.

A provisional diagnosis of auditory agnosia caused by bilateral destruction of auditory cortical structures due to ischaemic infarcts was made. Investigations over the next one-and-a-half years confirmed this diagnosis and showed the auditory agnosia to be of a predominantly verbal type. The patient experienced no improvement of auditory language comprehension and continued to be dependent on written communication.

INVESTIGATIONS

The following investigations are reported: neuroradiological, audiological, and neurophysiological; language status and nonverbal sound recognition; neurolinguistic and speech perceptual investigations.

Neuroradiological investigation

CT scans of the left and right hemisphere infarcts (fig. 2) were classified by comparing the individual slices with standard sections from an atlas for computerized tomography of the brain (Matsui and Hirano, 1978). Both the left and the right hemisphere lesions were middle cerebral artery infarcts, albeit with considerable differences in size and localization. The left hemisphere lesion involved the superior temporal gyrus and extended superiorly and anteriorly into the parietal lobe and the frontal lobe. The anterior extension overlay the central sulcus and the precentral and postcentral gyri. Posteriorly the lesion involved the supramarginal gyrus of the inferior parietal lobule and extended just onto the angular gyrus. The lesion included both the superior and middle temporal gyri. Involvement of the supratemporal plane with Heschl's gyri could be inferred reliably. The temporal isthmus containing geniculotemporal radiations was spared. The parietal part of the lesion did not extend deep enough to involve the area lateral to the posterior part of the lateral ventricle where the interhemisphere auditory pathways traverse (Rubens *et al.*, 1978; Damasio and Damasio, 1979).

The right hemisphere lesion was largely contained within the temporal lobe. The superior temporal gyrus carried the brunt of the lesion. Like the left hemisphere lesion it extended posteriorly onto the angular gyrus, but it was less well demarcated. Therefore, a massive destruction of the supratemporal plane including Heschl's gyri was uncertain. The geniculotemporal radiation through the temporal isthmus was not affected.

Comment. Given the nature and extent of the left and right hemisphere lesions, the patient's remaining auditory function is probably subserved for the most part by the right hemisphere auditory cortex. Note that this dependence on the right hemisphere already existed before the second stroke.

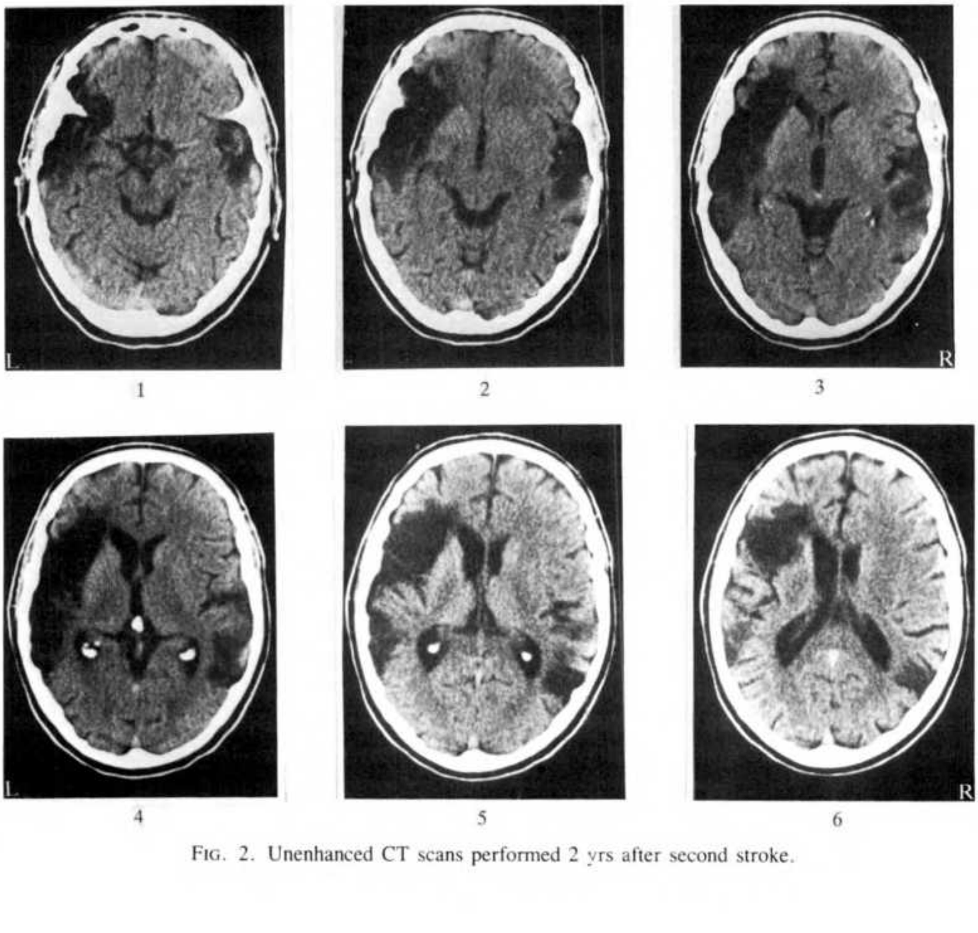

FIG. 2. Unenhanced CT scans performed 2 yrs after second stroke.

Audiological investigation

Standard pure tone audiometry demonstrated a minor bilateral sensorineural hearing loss, which exceeded 20 dB only at frequencies above 4000 Hz (Table 1).

TABLE 1 PURE TONE AUDIOMETRY

	Pure tone threshold (dB)	
Frequency (Hz)	*Left ear*	*Right ear*
250	10	20
500	10	15
1000	5	10
2000	5	10
4000	20	20
8000	40	45

Comment. The patient's mild hearing loss for higher frequencies was obviously not the cause of his auditory comprehension deficit.

Brainstem auditory evoked potentials

BAEPs were recorded on a Nicolet Pathfinder II. Stimuli were 0.1 ms clicks of 80 dB (SPL) presented monaurally at a rate of 11/s. The contralateral ear was masked with white noise. The filter setting allowed a bandpass of 150−3000 Hz. The potentials were recorded ipsilateral to the ear of stimulation from bipolar derivations Cz-A1 and Cz-A2.

Results. Left and right ear stimulation produced waveforms with identifiable peaks I−V, all latencies being within normal limits.

Comment. The results of tone audiometry and BAEPs indicate that the auditory afferent pathways up to the inferior colliculi were functioning normally.

Middle and long-latency auditory evoked potentials

Recordings of MLAEPs and LLAEPs were aimed at an evaluation of midbrain and telencephalic auditory pathways and structures. They were obtained with the same apparatus and stimuli and from the same recording sites as the BAEPs. The stimulation rate was 4.5/s and the bandpass 5−1000 Hz for MLAEPs and 0.25/s and 1−250 Hz for the LLAEPs.

Results. The Na component of the MLAEP was clearly present in the derivations contralateral and ipsilateral to the separately stimulated ears. The latencies were normal. This component was of smaller amplitude with right ear stimulation. The Pa component was also present in both derivations, but of smaller amplitude in the Cz-A1 derivation. Components P1, N1 and P2 of the LLAEP had normal amplitudes and latencies in all recordings. Ipsilateral and contralateral derivations showed nearly identical waveforms. The N2 and later components could not be identified reliably.

Comment. The generator sites of middle and long-latency auditory evoked potentials are still controversial. The study of patients with unilateral or bilateral temporal lesions has contributed little to resolve this issue. Bitemporal lesions have been found compatible with normal or nearly normal MLAEPs (Parving *et al.*, 1980; Woods *et al.*, 1984), while they can also be absent (Özdamar *et al.*, 1982). There is a similar lack of consistency regarding the LLAEPs, which have been reported normal (Parving *et al.*, 1980; Woods *et al.*, 1984; Tanaka *et al.*, 1987), delayed and of smaller amplitude (Albert *et al.*, 1972; Miceli, 1982), absent unilaterally (Auerbach *et al.*, 1982), and absent bilaterally (Michel and Peronnet, 1980) in patients with bitemporal lesions.

In an extensive review of reports of AEPs in patients with temporal lobe lesions, Woods *et al.* (1987) concluded that cortical lesions only affect the Pa generator if they extend beyond the classical auditory areas. They further observed that the N1 component was usually not abolished with lesions restricted to the superior temporal plane. The authors suggested that this component probably also has generators in the inferior parietal lobe. There is, however, evidence from neuromagnetic recordings (Hari *et al.*, 1980; Sams *et al.*, 1985) and from EP dipole source analysis (Scherg and von Cramon, 1986, 1990) that the exogenous middle and long-latency AEPs are generated in the auditory cortex.

The remarkably preserved AEPs in our case may be due to the presence of remnants of intact auditory cortex. Such remnants can produce normal evoked potentials in experimentally lesioned animals (Diamond and Neff, 1957). In addition, the posterior parts of the inferior parietal lobes, which according to Woods *et al.* (1987) have to be destroyed to annihilate the AEPs, may have contributed to their generation. Alternatively, it may be the case that the scalp-recorded potentials, although symmetric in distribution, are generated in the right hemisphere auditory cortex, which is obviously the least affected side. In summary, only the modest conclusion can be drawn that the presence of middle and late AEPs attests to the integrity of geniculotemporal radiations and at least some auditory cortical structures. Thus the evidence obtained from AEP investigations is compatible with the CT evidence.

LANGUAGE STATUS AND NONVERBAL SOUND RECOGNITION

Aachen Aphasia Test

The patient was tested using the Dutch version of the Aachen Aphasia Test (AAT) (Huber *et al.*, 1980, 1984; Weniger *et al.*, 1981; Willmes *et al.*, 1980, 1983). In addition to eliciting and recording a sample of spontaneous speech, the AAT has subtests for word and sentence repetition, written language, object and situation naming, and word and sentence comprehension. In the subtest on comprehension, patients have to select 1 picture out of 4 on the basis of auditory or visual input. The AAT further includes the shortened version of the Token Test (TT) (De Renzi and Vignolo, 1962; Orgass, 1976). The TT is usually presented auditorily. The TT was also presented visually using a test procedure introduced by Poeck and Hartje (1979). This procedure involves the test materials being screened off from view during the reading of each instruction. After 10 s (parts I–III) or 15 s (parts IV and V) the instruction was covered and the test materials were uncovered.

On several occasions before the second cerebrovascular lesion the patient had shown a stable pattern of performance on the AAT. The patient was tested again 3 months after his second stroke. In Table 2 these results are shown together with the last AAT before the second stroke. The interval between the tests was 23 months. There was an interval of 10 months between the auditory and the visual administrations of the TT after the second stroke.

Comment. The preliminary diagnosis of an auditory agnosia, in addition to the preexisting Wernicke's aphasia, was supported by the AAT results. The qualitative assessment of spontaneous speech, which takes into account semantic, syntactic and phonemic structure, articulation and prosody, automatized speech and communicative behaviour, found no changes compared with his status before the second stroke. Repetition changed dramatically. The performance deteriorated with growing complexity of the presented items (*see* Table 2) On written language the patient also performed worse than before the second stroke. But, as is shown in Table 2, this was almost entirely due to his inability to spell and to write to dictation, both mediated by the auditory modality. The comprehension part of the AAT demonstrated a dissociation between an almost unchanged written language comprehension and a considerably lower score on oral language comprehension. The performance on the auditory sentence comprehension part did not exceed chance level.

The pattern of results on the AAT obtained after the second stroke, in comparison with that before it, shows a selective disturbance of tasks that are dependent on the auditory modality. This modality bias also emerges from a discrepancy between the visual and auditory presentations of the Token Test (Table 3). The results obtained in the visual version show an error score that, according to the interpretation of the standard auditory test, is nonaphasic. Although the TT, like other subtests of the AAT, demonstrates a modality bias, it must be interpreted with caution. The performance on the visual TT was not only much better than the auditory TT results after the second stroke, but it was also superior compared with the auditory TT results before the second stroke. Since the visual TT is not a standardized test we consider the unambiguous change in performance on the comprehension part of the AAT the more reliable evidence of a modality specific change.

TABLE 2 AACHEN APHASIA TEST

	April 1986		*March 1988*		*Max. score*	
Repetition	87		30		150	
Phonemes		26		18		30
One-syllable words		25		9		30
Foreign words		21		3		30
Composits		6		0		30
Sentences		9		0		30
Written language	44		24		90	
Oral reading		25		24		30
Spelling to dictation		8		0		30
Words/sentences to dictation		11		0		30
Naming	85		91		120	
Objects (singular nouns)		23		30		30
Colours		29		30		30
Objects (composit nouns)		16		19		30
Situations (descriptions)		17		12		30
Comprehension	91		73		120	
Auditory (word)		23		20		30
Auditory (sentence)		24		10		30
Written (word)		25		26		30
Written (sentence)		19		17		30

TABLE 3 TOKEN TEST

	Error score (max. 50)	
Date	*Auditory*	*Visual*
April 1986	45	–
March 1988	42	–
January 1989	–	3

In sum, the AAT showed changes in comparison with the test results before the second stroke that can be attributed to a disturbance in the auditory reception of language. The patient's Wernicke's aphasia was essentially unchanged but compounded by an auditory deficit. Given its apparent central origin, this deficit was characterized as an auditory agnosia.

Nonverbal sound recognition

To test the patient's ability to recognize nonverbal sounds we applied a sound recognition test modelled after Spinnler and Vignolo (1966). It consisted of 20 environmental sounds recorded on tape (e.g., ambulance siren, electric razor, canary, trumpet, etc.). Each sound was presented in conjunction with 4 pictures representing the response alternatives. The correct response alternative pictured the actual source of the sound. The other 3 pictures represented the sources of an acoustically similar sound, an object or event semantically related to the source of the presented sound, or something unrelated. Failures to identify the correct picture were accordingly characterized as discriminative, semantic or odd failures. The mean time of presentation of each sound was 15 (range 8–28) s. Ten healthy control subjects (mean age 56, range 43–65 yrs) made between 1 and 5 incorrect responses (mean 3.2/20; 91% discriminative, and 9% semantic errors).

The original test of Spinnler and Vignolo was designed to investigate the nature of sound recognition deficits in aphasia. It consisted of 10 different sounds and was administered twice, the maximum score being 20. An abnormal score was established to be lower than 16. Spinnler and Vignolo detected sound recognition deficits mainly in severe Wernicke's aphasia. Semantic errors were far more frequent than discriminative errors. They concluded that sound recognition deficits in aphasia are associated with disorders of auditory verbal comprehension and are not perceptual discriminative, but associative in nature.

Results. Our patient was tested 7 wks after the occurrence of the second stroke. He performed 14/20 correct. Of the incorrect responses 4 were discriminative and 2 odd.

Comment. Our patient's score was slightly below normal performance. As the incorrect responses were mainly discriminative, we conjecture that the disturbed performance was due to the deficit acquired after the second stroke and not due to the pre-existing Wernicke's aphasia which, according to Spinnler and Vignolo, generally causes semantic errors.

NEUROLINGUISTIC INVESTIGATIONS

The specific changes in the AAT test profile demonstrated a clear dissociation between language comprehension in the auditory and visual modalities. In the presence of relatively preserved nonverbal sound recognition, this warranted the diagnosis of auditory verbal agnosia or word deafness. Further investigations were directed at the characterization of the underlying processing deficits.

Although the pure form of word deafness may be a fictitious entity (Buchman *et al.*, 1986), some of the most important studies on word deafness were carried out on relatively pure cases (Saffran *et al.*, 1976; Auerbach *et al.*, 1982) or on cases in which aphasic disturbances were temporary (Albert and Bear, 1974; Miceli, 1982; Tanaka *et al.*, 1987). In our case, however, Wernicke's aphasia already existed before the signs of word deafness developed. Is it also possible to attribute these later signs to the aphasia? The AAT results suggest that such is not the case. We contend that 'central' language mechanisms did not suffer further damage to the second cerebral infarct. This is supported by the results of a lexical decision task performed before and after the second stroke. These results are reported below, together with those of a syllable matching task and a task testing the ability to distinguish between sequences of Dutch and English words.

Lexical decision

Both before and after his second stroke the patient participated in a lexical decision experiment (Hagoort, 1989, 1990). The lexical decision task requires subjects to decide whether strings of letters or sounds are words of their language or not. In the original experiment words and nonwords were presented auditorily. The word targets consisted of Dutch words ranging from 1 to 4 syllables. Nonwords were matched in length and consisted of randomly selected Dutch syllables. The targets were preceded by primes, which were always words. A subset of the primes was semantically related to the word targets, while the remainder was unrelated. For our case, however, the primes are irrelevant. We will focus on the patient's number of correct and incorrect responses to the word and nonword targets. After the patient's second stroke the experiment was repeated. In addition, a visual version of the experiment was administered using the same target words and nonwords presented in written form, without primes.

Method. The targets consisted of 128 Dutch words and 128 nonwords, which were pronounceable according to the rules of the sound system in Dutch. Primes and targets were spoken by a female voice, tape recorded, and presented via headphones. The test session began with 20 starter trials to acquaint the subject with the procedure. For each target the patient had to decide whether it was a word or a nonword by pushing one of two buttons, a 'yes' button for words and a 'no' button for nonwords. For the visual version of the experiment the same targets were presented as a list, written in capitals, and the patient was asked to mark each target as a word or nonword.

Results. Before his second stroke the patient made errors on 4% of the auditorily presented targets. For the word targets, he always gave the correct response. For 7% of the nonwords, he incorrectly decided that they were words. After the second stroke the overall error percentage increased to 49% (30% for the words and 69% for the nonwords). In contrast, when the same targets were presented visually he responded without hesitation and made no errors.

Comment. The results indicate that the second stroke caused a specific deficit in accessing the auditory input lexicon, while access to the orthographic input lexicon was normal.

Distinguishing between languages

To investigate whether he was able to discriminate Dutch from a nonnative language on the basis of the auditory word form information, the patient, who had an active knowledge of English, was subjected to a test of randomly presented sequences of Dutch and English words.

Method. Twenty-four sequences of 15 bisyllabic and trisyllabic words each were presented. Twelve sequences consisted of Dutch words, and 12 of English words. The first sequence, consisting of Dutch words, was not scored. The stimuli were spoken by a female voice, tape recorded, and presented via headphones. After every sequence the tape was stopped by the experimenter, and the patient was asked to point to one of two cards, saying 'Dutch' and 'English'.

Results and comment. The results are presented in Table 4. The overall performance was above chance, the response being accurate in 17 out of 23 word sequences. However, closer inspection revealed that the patient was only accurate in identifying the English sequences (11/12), but performed at chance level for the Dutch ones (6/11). One explanation of this dissociation is that he used a response strategy in which uncertainty was resolved by choosing the response alternative 'English'. Alternatively, the patient might still have been able to extract certain salient phonetic characteristics of English that are not part of Dutch. Whatever the correct explanation for the dissociation between his performance for Dutch and English, the results suggest that he is no longer able to derive adequate phonetic representations from verbal acoustic input.

TABLE 4. ENGLISH-DUTCH LANGUAGE DISCRIMINATION

	Language of sequence		
	English	*Dutch*	*Total*
Response			
English	11	5	16
Dutch	1	6	7
Total	12	11	

Syllable matching

The patient's performance on the auditory lexical decision task established that he is no longer able to access the mental lexicon via the auditory route. This prevents him from recognizing spoken words. In the process of spoken word recognition the listener has to contact stored word forms in the auditory input lexicon. For this purpose, the listener has to extract contact representations from the speech signal (Frauenfelder and Tyler, 1987). These contact representations allow the activation of stored word forms that are consistent with the input. A number of different proposals have been made concerning the nature of these contact representations (e.g., Klatt, 1979; Mehler, 1981; Pisoni and Luce, 1987). Most likely they include information about the consonants and vowels composing a word and about the number of syllables and the stress pattern (Pisoni and Luce, 1987). To investigate whether the patient was still able to extract such a representation from the acoustic input, we applied a syllable matching task (P. Hagoort and A. Witjes, unpublished). This task requires a subject to construct some sort of phonological representation of presented word pairs and match the specified segments.

Method. In this task, pairs of bisyllabic words were presented. The list of word pairs consisted of two blocks, each including 60 target and 40 filler pairs. The first block contained 20 target word pairs with an identical first syllable (e.g., *fortuin-formaat*) (fortune-format) and 40 target pairs with no syllables overlapping (e.g., *laken-zebra*) (sheet-zebra). In the second block, 20 target word pairs were identical in their second syllable (e.g., *boeket-raket*) (bouquet-rocket). In addition, each block contained 40 filler pairs, 20 with identical first or second syllable and 20 without identical syllables. These pairs were constructed by combining the words from the target pairs in a different way. In this way, response strategies on the basis of the list structure were excluded (Hagoort, 1990). Each block started with 8 practice items. For the first block the patient was required to decide for each pair whether the words had the same first syllable. The pairs in the second block had to be judged for identity of the second syllable. The words were spoken by a female voice and played over closed headphones. There was an interval of 500 ms between the two words of a pair. The patient was given instructions in written form. He was asked to listen to each word pair and to indicate whether or not the words matched with respect to the specified syllable, by pointing to one of two cards saying 'same' and 'different'.

Results. The results for the two blocks were analysed separately. Only the responses on the 60 target items were analysed. To separate the patient's response bias from his sensitivity in this two-alternative forced-choice task, the nonparametric index of sensitivity A′ was computed. This measure is derived from signal detection theory (Green and Swets, 1966; Grier, 1971). The A′ value (e.g., 0.90) can be interpreted as the expected percentage correct (e.g., 90%) on a forced two-choice procedure. For the first block the patient's index of sensitivity (A′) was 0.86 (15/20 hits and 8/40 false alarms). For the second block his A′ was 0.87 (12/20 hits and 2/40 false alarms).

Comment. The patient turned out to be fairly accurate in matching the specified syllables of the auditorily presented word pairs. This implies that he is still able to extract at least a partial phonological representation from verbal acoustic input. Adequate performance in the syllable matching task probably only requires the presence of a very global phonological representation without detailed phonetic specifications (e.g., whether the onset consonant is a /b/ or a /p/). Given his severely impaired performance on the auditory lexical decision task the representation derived from the input, however, seems insufficiently specified to zoom in successfully on the appropriate word forms in the auditory lexicon.

In conclusion, the patient is clearly deficient in the ability to extract from the speech waves phonological representations specified well enough to allow him to recognize the words of his language. A deficit at the acoustic-phonetic level could be responsible for the impairment in constructing a fully specified phonological representation. The subsequent investigations thus focused on the patient's auditory verbal discrimination and identification abilities.

SPEECH PERCEPTUAL INVESTIGATIONS

The perception of speech sounds is usually tested using the 6 stop consonants /b/, /d/, /g/, /p/, /t/ and /k/ paired with a vowel (Saffran *et al.*, 1976; Auerbach *et al.*, 1982; Miceli, 1982; Tanaka *et al.*, 1987). These speech sounds have also been extensively used in dichotic listening research on hemisphere specialization of speech perception (Studdert-Kennedy and Shankweiler, 1970; Studdert-Kennedy *et al.*, 1972). The stop consonants tax the auditory-phonetic analysis in a particular way. Whereas vowels have a long steady state that makes them relatively easy to discriminate, the stop consonants are differentiated from one another by rapid formant transitions within about 50 ms from onset of the speech signal (Lieberman and Blumstein, 1988). This could make the perception of stop consonants particularly vulnerable to impairments of auditory temporal resolution. It is precisely this mechanism by which some authors have sought to connect impairments of general auditory processes to speech perception deficits (Tallal and Newcombe, 1978; Auerbach *et al.*, 1982; Miceli, 1982; Coslett *et al.*, 1984).

The contrasts between the stop consonants can be defined by two phonetic features, as illustrated in Table 5. Normal subjects discriminate more easily between speech sounds distinguished by two phonetic features (e.g., /b/ vs /t/) than between sounds distinguished by one feature (e.g., /b/ vs /d/) (Lieberman and Blumstein, 1988). If the discrimination of speech sounds by a patient demonstrates such a feature effect this might be interpreted as evidence that speech sound discrimination is still supported by phonetic processing capacities (Auerbach *et al.*, 1982).

We performed speech perceptual investigations very similar to those used in earlier case studies (Saffran *et al.*, 1976; Auerbach *et al.*, 1982; Tanaka *et al.*, 1987; Yaqub *et al.*, 1988). The results should provide a measure of the severity of the speech perceptual deficit and might also provide clues to its nature.

TABLE 5 ARTICULATORY FEATURES OF THE STOP CONSONANTS

	Place-of-articulation		
	Front (bilabial)	*Middle (alveolar)*	*Back (velar)*
Voicing			
Voiced	/b/	/d/	/g/
Unvoiced	/p/	/t/	/k/

1. *Discrimination of monosyllabic words*

As a first attempt at characterizing a possible speech perceptual deficit underlying the dissociation between auditory and written language comprehension, an auditory discrimination test was administered (Crul and Peters, 1976). The test consisted of 50 pairs of monosyllabic words, spoken by a female voice and recorded on tape. All words began and ended in consonants or consonant clusters. The words constituting a pair differed either in the word-initial or the word-final consonant (cluster) (27 pairs), or in the vowel (8 pairs). There were 15 pairs with identical words. The patient had to mark the response alternatives 'same' or 'different' on a response sheet.

Results. The test was performed at 3 and at 18 months after the second stroke with scores of 25/50 and 23/50 incorrect responses. Conversion into a nonparametric index of sensitivity gave A′ values of 0.67 and 0.58, respectively. The contingency tables (Table 6) illustrate an especially poor performance on words differing in vowel.

TABLE 6 DISCRIMINATION OF MONOSYLLABIC WORDS—CONTINGENCY TABLES*

	Stimulus			*Stimulus*		
	Different	*Identical*	*Total*	*Different*	*Identical*	*Total*
Responses						
Different	13 (2+11)	3	16	19 (2+17)	7	26
Identical	22 (6+16)	12	34	16 (6+10)	8	24
Total	35	15		35	15	

* The left and right-hand table represent, respectively, the performance at 3 and at 18 months after the second stroke. The numbers in parentheses indicate the responses on word pairs differing in vowel and the responses on pairs differing in consonant, respectively

2. *Vowel identification*

We tested vowel identification in a similar way to Auerbach *et al.* (1982). The patient was presented with a series of 100 vowels, /a/,/e/, /i/, /o/ and /u/, which were spoken by a male experimenter in random order. The lower half of the experimenter's face was covered to prevent lip-reading. On each trial, the patient marked 1 of the 5 response alternatives on an answer sheet.

Results. /a/, /e/, /i/,/o/ and /u/ were identified correctly, 5, 6, 8, 11 and 13 times out of 20, respectively. The total score of 43% correct identification was above chance (20%).

3. *Vowel identification; binary choice*

The patient was also tested with a forced binary choice procedure. A tape was prepared with 200 tokens of the 5 vowels /a/, /e/, /i/, /o/ and /u/ in random order. The interval between successive stimuli was 4 s. The stimuli were spoken by a female voice and presented through headphones. The length of the vowels ranged between 290 and 323 ms. The patient had an answer sheet with 200 numbered vowel pairs, one of each pair being the presented vowel. On the answer sheet, each vowel was paired with each of the other stimuli 40 times. The correct response alternative was randomly the first or the second member of the pair. The patient answered by marking one of the response alternatives.

Results. The patient's performance on this task is represented in Table 7. The average performance was 72.5% correct, which is above chance (50%).

TABLE 7 CONFUSION MATRIX OF VOWEL IDENTIFICATION—BINARY CHOICE

	Percentage responses				
	/a/	/e/	/i/	/o/	/u/
Stimulus					
/a/	87.5	7.5	2.5	2.5	0
/e/	7.5	80.0	7.5	5.0	0
/i/	7.5	12.5	65.0	2.5	12.5
/o/	15.0	7.5	2.5	62.5	12.5
/u/	7.5	5.0	10.0	10.0	67.5

4. *Vowel discrimination*

Vowel discrimination was tested employing the same stimuli as used in the vowel identification task. A tape was prepared with 200 vowel pairs. Between pairs there was an interval of 4 s and between members of a given pair an interval of 1 s. Half of the vowel pairs were identical. The stimuli were presented through headphones. The patient responded by marking 'same' or 'different' on an answer sheet after each presentation of a vowel pair.

Results. Results are presented in Table 8. The patient had a percentage of 92.0% correct responses. An A′ of 0.97 was computed from the overall proportions of hits (89/100) and false alarms (2/100).

TABLE 8 PROPORTION CORRECT DISCRIMINATION OF VOWELS

	/a/	/e/	/i/	/o/	/u/
/a/	1.00	1.00	1.00	1.00	1.00
/e/		1.00	0.30	1.00	1.00
/i/			0.95	1.00	0.90
/o/				0.95	0.70
/u/					1.00

5. *Consonant identification; binary choice*

Consonant identification and discrimination were evaluated using the stop consonants /b/, /d/, /g/, /p/, /t/ and /k/, paired with the vowel /a/. For the identification task a tape was prepared of 300 tokens of these 6 CV syllables, spoken by a female voice. There were pauses of 4 s between trials. The test procedure was similar to the one used in the vowel identification task.

Results. Table 9 presents the patient's performance on the consonant identification task. The average performance was 68.7% correct, which is above chance (50%).

TABLE 9 CONFUSION MATRIX OF CONSONANT IDENTIFICATION—BINARY CHOICE

	Percentage responses					
	/ba/	*/da/*	*/ga/*	*/pa/*	*/ta/*	*/ka/*
Stimulus						
/ba/	74	10	0	10	4	2
/da/	10	58	8	4	16	4
/ga/	0	0	82	4	6	8
/pa/	8	12	0	72	6	2
/ta/	4	2	0	4	84	6
/ka/	10	12	8	8	20	42

6. *Discrimination of stop consonants*

The tape for the discrimination task was constructed using the same stimuli as used in the CV identification task. The tape contained 420 pairs of CV syllables, half of which were identical. The 30 possible pairs of different stimuli were presented in random order, each 7 times. The test procedure was the same as the procedure used for the discrimination of vowels.

Results. Results are presented in Table 10. The average performance was 80.0% correct. The A′ computed was 0.87 (proportion hits 170/210, false alarms 45/210).

Comment. In speech perceptual tasks using isolated vowels or CV syllables, the perception of vowels was better than the perception of consonants. The difference in performance between the vowel and the CV discrimination tasks (tasks 4, 6) was significant at the 5% level, using the Mann-Whitney U test ($Z = 2.15$, $P<0.05$; two-tailed). Here, as elsewhere in this section, t tests performed on arcsine transformed scores yielded comparable results. There was a considerably smaller and not significant difference in performance on the corresponding identification tasks (tasks 3, 5) ($Z = 0.32$; $P = 0.75$; two-tailed). While, probably due to their longer duration and steady state, vowels were better discriminated than CV stimuli, the assignment of phonetic labels to vowels was apparently not better than to CV stimuli If the patient's speech perceptual disorder was entirely due to an acoustic deficit, it would be expected that the advantage of vowels in the discrimination task would be accompanied by a better identification of vowels compared with consonants. Since this was not so, an additional phonetic deficit seems likely.

TABLE 10 PROPORTION CORRECT DISCRIMINATION OF CV SYLLABLES

	/ba/	*/da/*	*/ga/*	*/pa/*	*/ta/*	*/ka/*
/ba/	0.91	0.86	0.93	0.36	1.00	0.93
/da/		0.71	1.00	1.00	0.36	0.79
/ga/			0.77	1.00	0.93	1.00
/pa/				0.71	0.86	0.79
/ta/					0.83	0.36
/ka/						0.77

The assumption that the acoustic properties of isolated vowels (i.e., their longer steady-state portion) accounted for their better discrimination is compatible with the finding that monosyllabic words differing in vowel did not seem to be discriminated at all (task 1). The perception of vowels in consonant contexts depends partly on the extraction of phonetic attributes of the signal, while isolated vowels can be processed on the basis of their acoustic attributes alone (Liberman *et al.*, 1967). Due to the additional phonetic specification, vowels in consonantal contexts are normally better identified than isolated vowels, in spite of a shorter steady-state portion (Strange *et al.*, 1976, 1979). The breakdown on vowels in a consonant context implies that the patient was highly sensitive to the steady state duration of vowels. But this sensitivity in turn might indicate that he was not able to use the phonetic cues adduced by the context, as in normal subjects duration is not decisive (Dwyer *et al.*, 1982). These results, therefore, cannot easily be reduced either to an acoustic or to a phonetic deficit, but rather suggest an interaction.

In testing consonant perception we used a CV identification task with a forced binary choice procedure similar to the task used by Auerbach *et al.* (1982), Tanaka *et al.* (1987), and Yaqub *et al.* (1988). Auerbach *et al.* and Yaqub *et al.* observed better performance in their patients when the two choice alternatives differed in two features than when they only differed in one. Presumably, to choose one of two response alternatives on hearing 1 CV syllable, a phonological representation is generated and compared with the phonological representations of the syllables that constitute the response alternatives. Feature effects may arise from this comparison (Baker *et al.*, 1981). If our patient's performance demonstrates a feature effect, this might indicate that he can still draw on phonetic processing capacities and is not only dependent on nonlinguistic auditory capacities. However, the difference between the performance on one-feature and on two-feature contrasts (65.0% vs 74.2%) was not significant ($Z = 0.86$, $P = 0.20$; two-tailed). The absence of a significant feature effect also suggests a deficit at the phonetic level.

In contrast to other authors who used the CV identification task with binary choice, we also used a discrimination task. Although in this task the percentage correct responses were significantly higher for stimulus pairs differing in two features than for the one-feature contrasts (95.3% vs 72.0%; $Z = 2.2$, $P < 0.05$; two-tailed), the performance between different one-feature contrasts diverged even more than between one and two-feature contrasts (*see* Table 11). Even an unambiguous feature effect, however, would not necessarily imply that the patient is able to process speech at the phonetic level, since in discrimination tasks this effect may also be attributed to the acoustic differences underlying the phonetic identity of the speech signals.

TABLE 11. SUMMARY OF CV IDENTIFICATION AND DISCRIMINATION (TASKS 5 AND 6)

Nature of phonetic distinction/ no. of contrasting features	*Identification (binary choice)*	*Discrimination*
Voiced/voiceless (1 distinctive feature)	56.7%	57.3%
Place-of-articulation for voiceless stops (1 distinctive feature)	61.7%	67.0%
Place-of-articulation for voiced stops (1 distinctive feature)	76.7%	93.0%
Voiced/voiceless and place-of-articulation (2 distinctive features)	74.2%	95.3%

A note is in order on the patient's poor discrimination of monosyllabic words and his fairly good detection of identical syllables in bisyllabic words. Most likely, this difference is explained by the fact that each of the monosyllabic word pairs differed in a single feature or sound contrast specially selected to detect difficulties in auditory discrimination (Crul and Peters, 1976). In the syllable matching task the words were not selected to have minimal sound contrast, but only such that they had (or had not) an identical first or second syllable. The difference in performance indicates that phonological representations can be constructed that include a syllabic breakdown of words, but that lack sufficiently distinctive phonetic specifications.

7. *CVC syllable identification and discrimination; synthetic speech*

In addition to the previous tasks using natural speech, the patient was investigated using synthetic speech. Identification and discrimination tests using synthetic speech stimuli have been developed to systematically investigate auditory and phonetic processes in speech perception (Liberman *et al.*, 1967). Similar tests have been used to investigate speech perception deficits in aphasia (Basso *et al.*, 1977; Blumstein *et al.*, 1977*b*, 1984; Yeni-Komshian and Lafontaine, 1983). The synthetic nature of the stimuli allows for control of the physical/acoustical dimensions that underlie the characterization of speech signals in terms of phonetic features. Whereas the phonetic feature voice, for example, distinguishes between /b/ (voiced) and /p/ (unvoiced) in a dichotomous way, the acoustical property voice-onset-time (VOT) underlying the distinction can be varied continuously. This principle is put to use in identification and discrimination tasks on VOT and place of articulation continua. Such tests consist of stimuli that span the acoustical distance between, for instance, /b/ and /p/ (VOT continuum) or /b/ and /d/ (place-of-articulation continuum) in a stepwise fashion. These tests have demonstrated that there is a remarkably well-defined boundary between stimuli on such a continuum labelled as one or the other speech signal by normal subjects. Normal subjects only discriminate accurately between stimuli that they can assign to different phonetic categories. Two stimuli from the same phonetic category but separated by a certain distance on the continuum are not discriminated at better than chance level, while 2 stimuli separated by the same distance and from different categories are. This phenomenon of categorical perception is central to the issue of whether or not the perception of speech requires special mechanisms (Repp, 1984; Kuhl, 1986). Our patient was submitted to synthetic speech tests for one VOT continuum (/b/-/p/) and two place-of-articulation continua (/p/-/t/ and /b/-/d/).

Materials and procedure. Starting from a naturally spoken Dutch CVC word /bak/, 4 meaningful Dutch CVC words were constructed. The procedure involved low-pass filtering (cut-off frequency 4 kHz, slope 24 dB/octave), digitization (10 kHz sampling rate), and storage in computer memory. Subsequently formants were extracted with LPC-analysis and root-solving procedure using the ILS programming package (ILS, 1978). Next, the signal was resynthesized, applying a pitch synchronous energy correction (Maassen and Povel, 1985). Because plosives and vocal murmur deteriorate after resynthesis from formants, /ak/ was resynthesized from reflection coefficients, and the /b/ plus vocal murmur of the original spoken /bak/ was spliced in initial position in the resynthesized /bak/. Total stimulus duration was 320 ms.

The VOT continuum (/bak/-/pak/) was constructed by changing VOT in 9 steps from −80 ms (i.e., 80 ms vocal murmur preceding the plosive) to +12 ms (i.e., no vocal murmur and a silent gap of 12 ms between plosive and vowel onset). Stimulus 7 had VOT = 0 ms. It should be noted that in Dutch the phoneme boundary between voiced and voiceless plosive cognates is different from that in English. The value around −20 ms that we found in normal subjects (*see* fig. 3) is consistent with previous reports (Lisker and Abramson, 1964; Slis and Cohen, 1969).

Two place-of-articulation continua (/bak/-/dak/ and /pak/-/tak/) were constructed by manipulating the second (F2) and third (F3) formant transitions. F2 started at 1000 Hz for the bilabial and at 2000 Hz for the alveolar plosive, and ended at 1200 Hz in the /a/. F3 transition starting values were 2500 Hz and 3100 Hz, respectively, and ending value 2000 Hz. By linear interpolation of F2 and F3,9 steps on the place continua were constructed. Transition duration was 40 ms for both F2 and F3. F1 increased from 200 Hz to 750 Hz in a much shorter transition duration (14 ms) in order to make the plosive character of the initial consonant more prominent, and to emphasize the voiceless cognate. The analysed signal was subsequently resynthesized as described above.

Identification tapes consisted of 90 stimuli for each continuum. Each stimulus was presented 10 times. The interval between successive stimuli was 3.3 s. Discrimination tapes contained 78 pairs, 42 of which differed by two steps on the continuum, and 36 that differed by 3 steps. In the /bak/-/pak/ and /pak/-/tak/ continua the intervals between pairs were 4.0 s and intervals between stimuli within pairs 2.3 s. In the second place-of-articulation continuum (/bak/-/dak/) the interstimulus interval within pairs was 960 ms.

The patient was tested in a quiet room on three different occasions. The stimuli were presented through headphones. In discrimination tasks, the patient responded by marking on an answer sheet the response alternative 'same' or 'different' In the identification tasks he had to mark the words constituting the response alternatives.

Results. The results are shown in fig. 3. The discrimination conditions shown are those with 3 steps between pair members. Except possibly for the /pak/-/tak/ continuum identification performance seems random. Discrimination performance is relatively preserved in the VOT continuum.

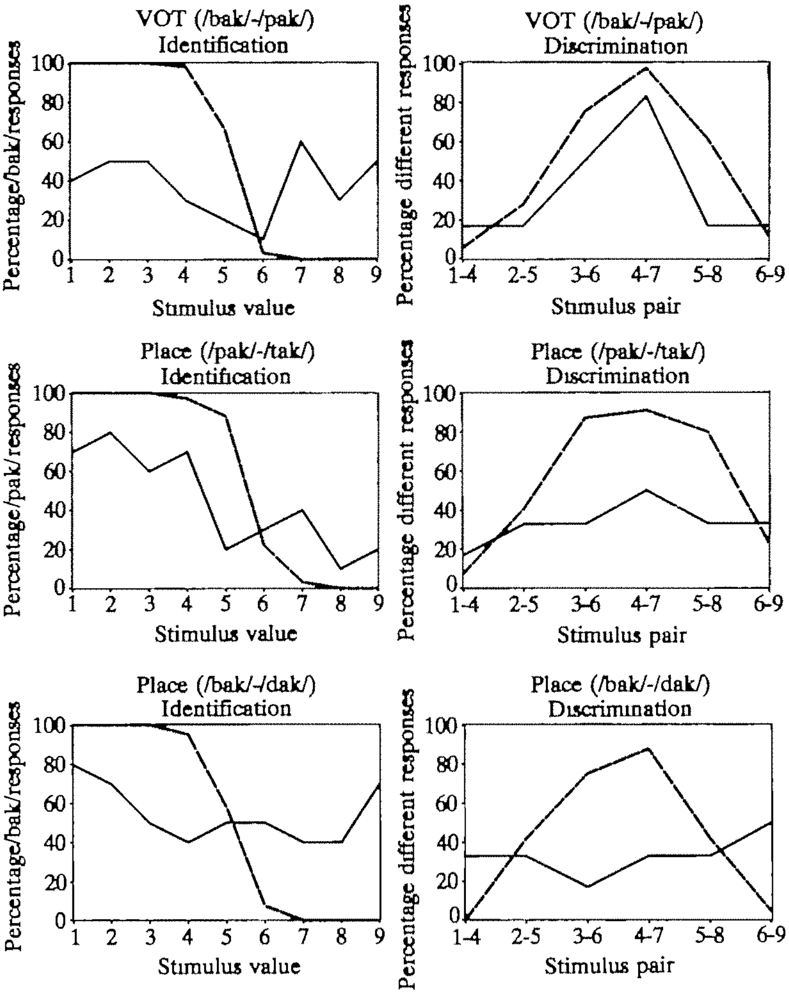

FIG. 3. Performance in identification and discrimination tasks on three different speech continua. Solid lines represent the patient's performance, dashed lines the averaged performance of 10 normal subjects.

Comment. From the severe impairment of both discrimination and identification performance, we inferred that there is probably a phonetic as well as an auditory component to the patient's speech perceptual disturbance. It could be argued that the impaired identification is fully determined by an inability to discriminate the stimuli, which might be attributed to an auditory deficit. This is not an adequate account, however, because discrimination on the VOT continuum was relatively preserved, while identification was random. The contrasting hypothesis that the pattern of results is due to a phonetic deficit only is equally unlikely. This possibility would be supported if the disturbance in identification performance had been accompanied by an intact discrimination (Yeni-Komshian and Lafontaine, 1983). Our patient's overall discrimination performance, however, was evidently impaired, which rules out this possibility.

The selectively preserved discrimination on the VOT continuum might be due to the perception of voicing differences being more readily mediated by general auditory mechanisms, as the feature voice is more closely tied to acoustically invariant properties than place-of-articulation (for critical discussion, *see* Summerfield, 1982). This explanation implies a deficit at the phonetic level. However, while in the synthetic speech tasks the voicing distinction was better perceived than the place contrast, the reverse was true using natural speech. Although differences between results obtained with natural speech and results obtained with synthetic speech are not uncommon in patients (Miceli *et al.*, 1982; Caramazza *et al.*, 1983), the discrepancy in our results cautions us not to overstate this argument (*see also* Addendum).

The speech perceptual investigations may be summarized by the conclusion that the patient's level of performance was comparable with that found in other cases of word deafness attributed to a speech perceptual deficit (Saffran *et al.*, 1976; Miceli, 1982; Auerbach *et al.*, 1982; Yaqub *et al.*, 1988). As to the pattern of performance, several findings argued against a reduction of the speech perceptual disorder to an auditory processing deficit only. (1) Discrimination of vowels was superior to the discrimination of consonants, while identification of vowels and consonants was not significantly different, though more severely impaired. This dissociation between discrimination and identification performance argues for a phonetic deficit. (2) The better discrimination of isolated vowels compared with consonants was not mirrored in the discrimination of monosyllabic words differing either in (medial) vowel or in a consonant. Since vowels in a consonantal context have a shorter steady-state portion, this might be explained in terms of an auditory deficit. But in view of evidence that consonantal context provides additional phonetic specification that aids vowel recognition, a phonetic deficit has to be assumed to explain the apparent inability to use these cues and, thereby, the strong dependence on steady-state duration of vowels. (3) The absence of a significant feature effect in CV identification with binary choice and the lack of an unambiguous feature effect in CV discrimination implies that recognition of these sounds is mainly dependent on nonlinguistic auditory capacities. (4) In the presence of a relatively preserved discrimination on the VOT continuum, the otherwise severe disturbance of identification and discrimination on synthetic speech continua indicates that both auditory and phonetic levels of speech perception are affected.

Taken together, these results point to a combination of auditory and phonetic impairments. The strength of this conclusion, however, is limited by the fact that auditory and phonetic deficits cannot be assessed independently given that the auditory processes essential to speech perception are largely unknown. Also, the results do not allow any firm statement with respect to the relative contributions of the two types of impairment.

SUMMARY OF MAJOR FINDINGS

The patient we studied suffered a left hemisphere stroke and acquired a Wernicke aphasia at the age of 54 yrs. Three years later, a right hemisphere stroke caused severe deterioration of auditory language comprehension while the patient's language expression remained unchanged. The recognition of environmental sounds was only mildly impaired.

The left hemisphere infarct was located temporoparietally and involved most of the superior temporal gyrus. It probably left the geniculotemporal radiation intact. The right hemisphere infarct was smaller. It also involved the superior temporal gyrus and extended posteriorly, like the left hemisphere infarct, onto the angular gyrus. The auditory radiation through the temporal isthmus was spared.

Pure tone audiometry and BAEPs established intact auditory afference up to the midbrain. Middle and long-latency auditory evoked potentials could be elicited both with left and right ear stimulation. A slight asymmetry in the Pa component was consistent with CT evidence of greater destruction of the left hemisphere auditory cortex. The P1, N1 and P2 deflections were essentially normal, suggesting that the auditory cortices might contain some intact remnants.

Comparison of patient's performance on the Aachen Aphasia Test before and after his second stroke confirmed that only auditory comprehension had suffered, while performance on tasks not dependent on the auditory input channel was unchanged. The performance on an auditory lexical decision task was nearly normal prior to the second stroke, but random after it. When the same targets were presented visually, he made no errors. Furthermore, the patient could not distinguish auditorily presented Dutch words from English words very well. On a syllable matching task, however, he showed a fairly good performance. This suggested that he was still able to extract some sort of phonological representation from the acoustic-phonetic input, including a syllabic breakdown of the words.

Further investigations focused on speech perceptual abilities, revealing an impairment of phoneme identification and discrimination using monosyllabic words, vowels and CV syllables. The voicing contrast was perceived less well than the place-of-articulation contrast. The performance on synthetic speech tasks using place-of-articulation and voice-onset-time continua was also severely disturbed. Only discrimination of stimuli on the VOT continuum showed a preserved phoneme category boundary. The overall pattern of results provided arguments for a speech perceptual disturbance to which both general auditory and phonetic deficits seem likely to contribute.

GENERAL DISCUSSION

In many cases of pure word deafness that have been reported, the syndrome was accompanied by aphasic disturbances (Goldstein, 1974; Buchman *et al.*, 1986). Most case reports, however, do not explicitly take issue with the presence of aphasic symptoms and treat them as merely contaminating the word deafness. The possibility of an underlying deficit that contributes both to the aphasic disturbance and to the word deafness in these patients is rarely considered (*but see* Caramazza *et al.*, 1983; Franklin, 1989). The patient we studied is a rare instance of the coexistence of aphasia with word deafness, in that the aphasia already existed and was documented at the time the patient acquired word deafness. The word deafness could, therefore, clearly be distinguished from the aphasia. This does not preclude a deficit related to the aphasia also being relevant to the word deafness. Surely the word deafness of our patient would not have occurred if the right hemisphere stroke had not been preceded by one in the left hemisphere.

The nature of the left hemisphere's contribution to word deafness will be our main focus in this discussion. In the analysis of our case, we chose to distinguish auditory and phonetic stages of speech perception, since earlier case reports claimed a specific deficit at either one or the other level (Saffran *et al.*, 1976; Auerbach *et al.*, 1982; Yaqub *et al.*, 1988). While we suggested a mixed deficit, the arguments we provided are not incontrovertible, given the fact that there is no generally accepted account of how auditory and phonetic processes are related, let alone a way to assess auditory and phonetic deficits independently. However, as we will discuss below, the left hemisphere specialization of phonetic processing capacities and the explanation of word deafness as a disconnection syndrome favour a mixed deficit rather than a pure auditory or phonetic deficit. We further discuss how this ties in with present knowledge on speech perceptual deficits in aphasia.

Auditory vs speech modes of perception

The distinction between auditory and phonetic levels or modes of perception originates partially in research on categorical perception (Liberman *et al.*, 1967). Recent developments in categorical perception research, such as the use of animal models and the demonstration that nonspeech sounds can be categorically perceived, have changed the field, but not eliminated the distinction (Repp, 1984; Kuhl, 1986). Of particular interest to the present discussion is the support for the distinction from studies on hemispheric specialization using dichotic presentation of speech stimuli (for a review, *see* Tartter, 1988). Ear asymmetries obtained in dichotic studies have been interpreted as due to hemisphere asymmetries in processing capacities. Since stop consonants display a right ear advantage not displayed by vowels, it has been suggested that consonants require a speech mode of perception, which is left hemisphere based, while vowels can be processed in both hemispheres by general auditory mechanisms (Studdert-Kennedy and Shankweiler, 1970; Studdert-Kennedy *et al.*, 1972). Evidence from patients with hemisphere lesions and evidence from split-brain research also indicate that phonetic processing capacities are, indeed, unique to the left hemisphere (Oscar-Berman *et al.*, 1975; Zaidel, 1976; Levy and Trevarthen, 1977). Finally, animal data suggesting a left hemisphere specialization for species-specific calls provide circumstantial evidence for the engagement of left hemisphere specialized processes in speech perception (Petersen *et al.*, 1978; Miller and Jusczyk, 1989).

The distinction between auditory and speech modes of perception has been invoked by several authors to explain the dissociation between verbal and nonverbal auditory agnosia (Albert *et al.*, 1972; Albert and Bear, 1974; Lambert *et al.*, 1989). Although most patients that have been reported displayed difficulties in both verbal and nonverbal sound recognition (Gazzaniga *et al.*, 1973; Chocholle *et al.*, 1975; von Stockert, 1982; Miceli, 1982; Buchtel and Stewart, 1989), the occurrence of relatively pure cases does support a double dissociation (Lambert *et al.*, 1989). The distinction between auditory and speech modes of perception might indeed be relevant to the explanation of this dissociation. However, the way it was applied so far merely restated the observation that the processing of speech and nonspeech sounds diverge at some level, and did not elucidate the functional loci of verbal and nonverbal auditory agnosia.

The distinction between auditory and speech modes of perception has also been invoked to account for different patterns of deficits in word deafness. Auerbach *et al.* (1982) argued that the speech perceptual deficit encountered in word deafness must be considered prephonetic if it can be attributed to a disorder in acoustic processing. He specified this acoustic deficit as a disorder of temporal auditory acuity, to be demonstrated by psychoacoustic measures like click-counting and click-fusion. While this deficit is localized at a prelinguistic level, it has its major manifestation at a linguistic level, as the auditory temporal resolution suffices for the perception of nonverbal sounds but is insufficient to resolve the rapid acoustic transients characteristic of certain speech sounds. Auerbach *et al.* formulated a number of criteria that purportedly distinguish patients with a deficit at the acoustic (prelinguistic) level from patients with a deficit at the phonetic (linguistic) level. While they described a case of the former type, a well-documented case that fits the latter type has been reported by Saffran *et al.* (1976).

The model proposed by Auerbach *et al.* (1982) connects the distinction between phonetic and acoustic deficits in word deafness with the lesion type being unilateral or bilateral. It associates the acoustic type of deficit with bitemporal lesions ('type I word deafness') and the phonetic deficit with unilateral left hemisphere lesions ('type II word deafness'). Thus the model offers an explanatory scheme that relates deficits at different stages of processing to distinct lesion patterns. We want to argue in the next section, however, that the distinction between acoustic and phonetic deficits in word deafness must be dissociated from the distinction between unilateral and bilateral cases.

The explanation of pure word deafness as a disconnection syndrome

Pure word deafness has long been recognized as a sequel either to a left hemisphere temporal lobe lesion or to bilateral temporal lobe lesions (Schuster and Taterka, 1926; Geschwind, 1965). The explanation of pure word deafness as a disconnection syndrome (Geschwind, 1965) unifies unilateral and bilateral cases in that it assumes that in unilateral cases the lesion extends deep subcortically and involves the interhemispheric auditory pathways. This explanation is strengthened by evidence from dichotic listening studies which elucidated the functional significance of interhemispheric auditory connections. Sparks and Geschwind (1968) established that sectioning the corpus callosum results in an almost complete suppression of left ear dichotic verbal information. This finding confirmed that left ear dichotic verbal information, arriving in the right hemisphere auditory cortex, has to be transferred to the left hemisphere by commissural auditory fibres in order to be processed as language.

The disconnection explanation of pure word deafness also derives support from neuroradiological studies (Rubens *et al.*, 1978; Damasio and Damasio, 1979), which demonstrated that patients with left hemisphere lesions and a left ear extinction in verbal dichotic listening tasks have a consistent pattern of lesions extending deep to the wall of the lateral ventricle. It can be concluded that unilateral left hemisphere lesions may indeed cause damage to the interhemispheric auditory pathways and deprive the left hemisphere of auditory input via this pathway. According to Geschwind's disconnection theory, a lesion of this type may have the same effect on language function as bilateral temporal lobe lesions.

Most of the case reports published in the last decade, including Auerbach *et al.* (1982), subscribe to a disconnection type of explanation of pure word deafness. But whereas the disconnection hypothesis unifies unilateral and bilateral cases in a single explanation, Auerbach *et al.* chose to subdivide the syndrome again into two distinct types. It is unclear how Auerbach *et al.* intended their adherence to the disconnection hypothesis to be reconciled with their subdivision of pure word deafness into different types. Since the disconnection hypothesis implicates both auditory cortices in the causation of word deafness (either by direct lesion involvement or by a disconnection), a classification of word deafness into auditory and phonetic types cannot be based on the differential specialization of left and right auditory cortex. This does not imply that unilateral and bilteral cases must be identical in all respects. Whereas only bilateral cases seem to go through an initial episode of cortical deafness (Mendez and Geehan, 1988), unilateral cases may be more frequently accompanied by aphasic symptoms, purely contingent on the considerable extension of a lesion which, according to the disconnection hypothesis, must involve the interhemispheric auditory connections and the auditory cortex at the same time.

Mixed deficits in word deafness

In our view, a classification of word deafness as acoustically or phonetically based bears no relation to the lesion being unilateral or bilateral. In addition, the dichotomous classification itself may be criticized on several grounds.

First, the acoustic deficit documented in bilateral cases might also be present in patients with unilateral lesions. We know of only one unilateral case in which the presence of acoustic deficits was investigated (Albert and Bear, 1974). This patient evidenced an impairment of auditory temporal resolution only slightly milder than that displayed by the bilateral case of Auerbach *et al.* (1982).

A second reason for questioning the proposed classification of word deafness is the improbability of an acoustic deficit as the only cause of the syndrome in all bilateral cases. A recent case report carefully documented a severe psychoacoustic deficit in a patient with bilateral lesions (Tanaka *et al.*, 1987). We suspect that even the severe deficit of this case only caused word deafness because it occurred together with a higher level deficit. This patient had gradually recovered from Wernicke's aphasia due to a left temporal lobe lesion when she experienced a right hemisphere stroke that caused word deafness. The authors documented deficits in temporal resolution (Albert and Bear, 1974) and in temporal sequencing (Efron, 1963; Swisher and Hirsh, 1972). However, these deficits were not limited to the auditory modality, but also encompassed the visual and somatosensory modalities. A supramodal temporal sequencing disorder seems to be associated with left hemisphere lesions that cause aphasia, though not with left hemisphere lesions as such (Efron, 1963). The presence of this supramodal deficit suggests persistent effects due to the left hemisphere lesion, in spite of the patient's reported recovery from aphasia. Furthermore, for an acoustic deficit one would predict vowel perception to be better than consonant perception, consistent with the criteria formulated by Auerbach *et al.* (1982). The patient's performance was indeed slightly better on vowels, but at the same time the recognition of nonverbal sounds was only mildly disturbed. We would have expected that an auditory processing disorder that severely disrupts vowel perception would also strongly affect the recognition of environmental sounds. In sum, these features of the case reported by Tanaka *et al.* (1987) provide reasons to express doubts on an auditory processing deficit as the only cause of this patient's word deafness.

The main thrust of this discussion is that most patients are not sufficiently documented to allow a classification according to the dichotomous scheme proposed by Auerbach *et al.* (1982). Moreover, evidence can be gathered from recent literature amounting to counter-examples to the proposed explanatory scheme. This prepares the ground for an alternative hypothesis that implies the involvement of auditory as well as phonetic processes in the causation of word deafness. The findings in our own case, indicating a mixed deficit rather than an isolated acoustic or phonetic deficit, are consistent with the proposed hypothesis. The way word deafness evolved from Wernicke's aphasia in our patient may further elucidate the hypothesis.

A remarkable feature of our patient is the fact that the change in his language status, caused by the right hemisphere infarct, was limited to the auditory input modality, as demonstrated by the AAT results before and after the second vascular accident. The second stroke did not even cause temporary changes outside the domain of the auditory recognition disturbance. This indicates that the patient's residual language capacities after his first stroke were still subserved by the damaged left hemisphere, which was only dependent on the right hemisphere for transfer of auditory information. Presumably the severe involvement of the left hemisphere auditory structures compromised the left hemisphere specialized processes that support phonetic analysis. This did not result in specific speech perceptual difficulties as long as general auditory processes subserved by the right hemisphere functioned adequately, given that intact interhemispheric connections allowed an interplay between the two hemispheres. The subsequent involvement of the right hemisphere auditory cortex, then, sufficiently degraded the auditory input to linguistic processing stages that a specific speech perceptual deficit, that is, word deafness, resulted. We thus suppose that, before the second stroke, the patient was already partially dependent on nonlinguistic auditory capacities to compensate for deficient phonetic processing.

The interpretation we propose of our case might apply more generally. We suggest that word deafness is caused by deficits both of phonetic processes and of nonlinguistic general auditory capacities. This hypothesis strongly relies, first, on the disconnection hypothesis as an account of the underlying neurological events, and, secondly, on the left hemisphere's specialization for phonetic analysis. These two elements do not in all respects fit together, however. Whereas the disconnection hypothesis makes word deafness conditional on bilateral lesions or a disconnection, it is unclear why, given the existence of specialized phonetic processes for speech perception, a selective disturbance of these processes by a left hemisphere lesion does not suffice to produce severe speech perceptual problems. Evidence relevant to this issue can be obtained from the study of speech perceptual deficits in aphasia.

Speech perceptual deficits in aphasia

In spite of the evidence we have already cited in favour of left hemisphere specialized capacities for phonetic analysis, the disconnection explanation of word deafness could make one more inclined to take both hemispheres for equipotential in this respect, or even doubt the existence of special mechanisms for phonetic analysis. The question to be dealt with in this section is therefore whether studies on speech perceptual deficits in aphasia support left hemisphere specialized phonetic processes.

One study by Oscar-Berman *et al.* (1975) explicitly addressed phonetic processing in left and right hemisphere-damaged patients. It was found that left hemisphere patients, in contrast to right hemisphere patients, were impaired in the use of a phonetic code in identification tasks using dichotically presented CV syllables. These results support a distinction between auditory and phonetic levels of speech processing and strongly suggest that it is the left hemisphere that is specialized for the conversion of auditory parameters of speech into phonetic attributes.

The majority of studies pertinent to the issue have focused on the question to what extent speech perceptual deficits contribute to auditory language comprehension impairments in aphasia. These studies have in large part been motivated by the claim by Luria (1970) that the comprehension deficit of Wernicke's aphasia should be attributed to a specific impairment of phonetic analysis. A number of studies using phoneme identification and discrimination tasks have found perceptual difficulties but have failed to show a consistent relation between speech perception and auditory language comprehension (Basso *et al.*, 1977; Jauhiainen and Nuutila, 1977; Blumstein *et al.*, 1977*a*, *b*, 1984). Other studies found only a weak relation (Varney and Benton, 1979; Varney, 1984; Miceli *et al.*, 1980; Yeni-Komshian and Lafontaine, 1983; Riedel and Studdert-Kennedy, 1985). It thus appears that impairments in phonetic perception that can be demonstrated in aphasia are not a major factor in aphasic disturbances of auditory language comprehension. However, the results do not refute the original assumption that there are specialized left hemisphere mechanisms for phonetic analysis. This is supported, first, by the fact that right hemisphere-damaged subjects evidenced no deficit in phoneme perception (Goldblum and Albert, 1972; Basso *et al.*, 1977; Blumstein *et al.*, 1977*b*; Varney and Benton, 1979). In addition, a number of studies consistently found Wernicke's aphasics worse than other aphasia types on phoneme perception tasks (Goldblum and Albert, 1972; Blumstein *et al.*, 1977*b*; Baker *et al.*, 1981). This might be related to temporal lobe damage and concurrent involvement of auditory cortical structures that presumably underlie phonetic processing capacities. Finally, in some studies that explored categorical perception in aphasia, phoneme discrimination was better preserved than identification performance (Blumstein *et al.*, 1977*b*; Riedel and Studdert-Kennedy, 1985), that is, a dissociation that argues for an impairment of phonetic perception (Yeni-Komshian and Lafontaine, 1983; Riedel and Studdert-Kennedy, 1985). In short, these studies on speech perception and auditory language comprehension in aphasia are compatible with the existence of a specialized phonetic competence subserved by the left hemisphere.

The puzzling fact that remains to be explained, then, is why a disturbance of phonetic perception by a left hemisphere lesion contributes so little to impairments of auditory language comprehension in aphasia. Part of the answer is provided by work conducted by Blumstein and coworkers. Whereas most investigations referred to in the last paragraph set out to isolate speech perceptual deficits from higher level language impairments, Baker *et al.* (1981) and Milberg *et al.* (1988) also addressed the question of whether speech perceptual deficits interacted with semantic impairments and the process of lexical access. These studies suggested an intimate interaction between phonological and semantic factors in auditory word processing. More specifically, the first study indicated that perceptual deficits may become manifest with increased semantic demands, even if they are not evident in perceptual tasks. Thus there might be a small but more pervasive influence of speech perceptual deficits on auditory language comprehension in aphasia than earlier investigations suggested.

Within a modular framework, Blumstein (1987) summarized the investigations referred to above by stating that the speech perception system, that is, the phonetic/phonological processor, is not functionally autonomous since it can be affected by higher level language impairments. Our conjecture that word deafness might be due to an interaction of auditory and phonetic deficits emphasizes the obvious possibility that it can also be affected by lower level auditory impairments. This proposal is in some sense complementary to Blumstein's view. The relatively selective disturbance of speech perception in word deafness seems difficult to account for in purely auditory terms, given that neither auditory temporal resolution, nor any other auditory process can be singled out as crucial to intact speech perception. The evidence from aphasia on the other hand makes clear that, while left hemisphere lesions can cause speech perceptual deficits, these deficits alone do not account for major impairments of auditory language comprehension. Therefore, the hypothesis of a mixed deficit in word deafness might be in better agreement with our present knowledge of auditory cortical function than the hypothesis of isolated acoustic or phonetic deficits.

CONCLUSIONS

The present conception of word deafness is far removed from the original conception of the agnosias as central disturbances of recognition (Bauer and Rubens, 1985). Like many patients reported in recent decades, our patient had a speech perceptual disturbance of sufficient severity to explain the word deafness. The documentation on his language status before and after his second stroke rules out that changes occurred other than those related to the disturbance of the auditory input channel. The very discrete change in the language status, occasioned by the right temporal lobe infarction, strongly suggests that, apart from auditory input via the right hemisphere, there had been no compensation of any importance of left hemisphere language functions by the right hemisphere, since in this case a more general change should be expected.

The nature of the speech perception impairment in our patient does not fit in well with the hypothesis of Auerbach *et al.* (1982), stating that speech perceptual disturbances in word deafness can be classified as due to either a prephonetic, acoustic deficit or a deficit at the linguistic level of phonetic perception. In contrast to the proposal by Auerbach *et al.*, we conjecture that word deafness is due to an interaction between an impairment of general auditory processes and a deficit at the level of phonetic analysis. The presence of deficits at both these levels is coherent with the left hemisphere specialization of phonetic processing capacities and with the necessary involvement of both auditory cortices (by direct lesion involvement or by a disconnection) in word deafness.

Evidence from aphasia, reviewed by Blumstein (1987), suggests that a deficit at the level of phonetic analysis gives rise to a disturbance of auditory language comprehension only in the presence of a higher level language deficit. Similarly, according to our hypothesis, a deficit at the phonetic level gives rise to a manifest disorder of speech perception only if it is compounded with a lower level deficit of general auditory processes, that is, when a left temporal lobe infarct extends deep enough to involve interhemispheric auditory fibres, or when it is accompanied by a right temporal lobe infarct. This implies that speech perceptual processes, in spite of their left hemisphere specialization, are quite robust in the face of left hemisphere damage.

ADDENDUM

An anonymous reviewer proposed that the preserved discrimination of /bak/-/pak/ might be due to an artificial cue caused by the fact that the voiced and voiceless stimuli had different proportions of original and resynthesized speech. We investigated the possibility that voiceless stimuli sounded more unnatural than voiced stimuli by presenting 8 normal subjects with the same stimuli as used in the identification tasks on the VOT continuum and the two place-of-articulation continua. The subjects, who were naive with respect to synthetic speech continua, were asked to rate the 'naturalness' of the stimuli on a 5 point scale, ranging from −2 to +2. Prior to analysis, the 5 response categories were combined into 3 categories (unnatural, neutral, natural). The results demonstrated no difference in the percentage 'neutral' responses on the three continua (6%, 4% and 4%). The percentage 'natural' responses for each stimulus of the three continua is represented in fig. 4. The response patterns on the two place-of-articulation continua show, not unexpectedly, that the stimuli at the ends of the continua were most frequently rated as natural. The VOT continuum diverges from this pattern, but the stimuli at the voiced extreme of the continuum are not rated more frequently as natural than the stimuli at the voiceless extreme. Therefore, the pattern that would be expected if the suggested explanation for the preserved discrimination on the VOT continuum were right, was not obtained.

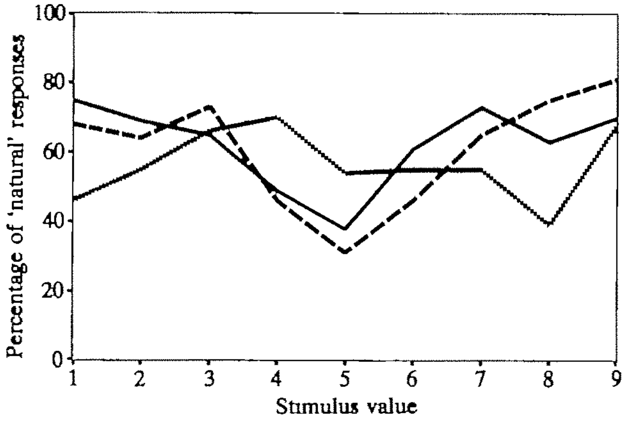

Fig. 4. Naturalness ratings by 8 normal subjects of the stimuli used in 1 VOT continuum and 2 place-of-articulation continua Hatched line = bak-pak; broken line = pak-tak, continuous line = bak-dak

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REFERENCES

Albert ML, Sparks R, von Stockert T, Sax D (1972) A case study of auditory agnosia: linguistic and non-linguistic processing. *Cortex*, **8**, 427–443.

Albert ML, Bear D (1974) Time to understand: a case study of word deafness with reference to the role of time in auditory comprehension. *Brain*, **97**, 373–384.

Auerbach SH, Allard T, Naeser M, Alexander MP, Albert ML (1982) Pure word deafness: analysis of a case with bilateral lesions and a defect at the prephonemic level. *Brain*, **105**, 271–300.

Baker E, Blumstein SE, Goodglass H (1981) Interaction between phonological and semantic factors in auditory comprehension. *Neuropsychologia*, **19**, 1–15.

Basso A, Casati G, Vignolo LA (1977) Phonemic identification defect in aphasia. *Cortex*, **13**, 85–95.

Bauer RM, Rubens AB (1985) Agnosia. In: *Clinical Neuropsychology*. Second edition. Edited by K. M. Heilman and E. Valenstein. New York and Oxford: Oxford University Press, pp. 187–241.

Blumstein SE (1987) Speech perception and modularity: evidence from aphasia. In: *Motor and Sensory Processes of Language*. Edited by E. Keller and M. Gopnik. Hillsdale, NJ: Lawrence Erlbaum, pp. 257–275.

Blumstein SE, Baker E, Goodglass H (1977*a*) Phonological factors in auditory comprehension in aphasia. *Neuropsychologia*, **15**, 19–30.

Blumstein SE, Cooper WE, Zurif EB, Caramazza A (1977*b*) The perception and production of voice-onset time in aphasia. *Neuropsychologia*, **15**, 371–383.

Blumstein SE, Tartter VC, Nigro G, Statlender S (1984) Acoustic cues for the perception of place of articulation in aphasia. *Brain and Language*, **22**, 128–149.

Buchman AS, Garron DC, Trost-Cardamone JE, Wichter MD, Schwartz M (1986) Word deafness: one hundred years later. *Journal of Neurology, Neurosurgery and Psychiatry*, **49**, 489–499.

Buchtel HA, Stewart JD (1989) Auditory agnosia: apperceptive or associative disorder? *Brain and Language*, **37**, 12–25.

Caramazza A, Berndt RS, Basili AG (1983) The selective impairment of phonological processing: a case study. *Brain and Language*, **18**, 128–174.

Chocholle R, Chedru F, Botte MC, Chain F, Lhermitte F (1975) Etude psychoacoustique d'un cas de 'surdité corticale'. *Neuropsychologia*, **13**, 163–172.

Coslett HB, Brashear BR, Heilman KM (1984) Pure word deafness after bilateral primary auditory cortex infarcts. *Neurology, Cleveland*, **34**, 347–352.

Crul Th, Peters H (1976) *Auditive Discriminative Test. Handleiding*. Amsterdam: Swets and Zeitlinger.

Damasio H, Damasio A (1979) 'Paradoxic' ear extinction in dichotic listening: possible anatomic significance. *Neurology, New York*, **29**, 644–653.

De Renzi E, Vignolo LA (1962) The Token Test: a sensitive test to detect receptive disturbances in aphasics. *Brain*, **85**, 665–678.

Diamond IT, Neff WD (1957) Ablation of temporal cortex and discrimination of auditory patterns. *Journal of Neurophysiology*, **20**, 300–315.

Divenyi PL, Robinson AJ (1989) Nonlinguistic auditory capabilities in aphasia. *Brain and Language*, **37**, 290–326.

Dwyer J, Blumstein SE, Ryalls J (1982) The role of duration and rapid temporal processing on the lateral perception of consonants and vowels. *Brain and Language*, **17**, 272–286.

Efron R (1963) Temporal perception, aphasia and déjà vu. *Brain*, **86**, 403–424.

Franklin S (1989) Dissociations in auditory word comprehension; evidence from nine fluent aphasic patients. *Aphasiology*, **3**, 189–207.

Frauenfelder UH, Tyler LK (1987) The process of spoken word recognition: an introduction. *Cognition*, **25**, 1–20.

Gazzaniga MS, Velletri Glass A, Sarno MT, Posner JB (1973) Pure word deafness and hemispheric dynamics: a case history. *Cortex*, **9**, 136–143.

Geschwind N (1965) Disconnexion syndromes in animals and man. Parts I and II. *Brain*, **88**, 237–294, 585–644.

Goldblum MC, Albert ML (1972) Phonemic discrimination in sensory aphasia. *International Journal of Mental Health*, **1**, 25–29.

Goldstein MN (1974) Auditory agnosia for speech ('pure word-deafness'): a historical review with current implications. *Brain and Language*, **1**, 195–204.

Green DM, Swets JA (1966) *Signal Detection Theory and Psychophysics*. New York and London: John Wiley.

Grier JB (1971) Nonparametric indexes for sensitivity and bias: computing formulas. *Psychological Bulletin*, **75**, 424–429.

Hagoort P (1989) Processing of lexical ambiguities: a comment on Milberg, Blumstein, and Dworetzky (1987). *Brain and Language*, **36**, 335–348.

Hagoort P (1990) *Tracking the Time-course of Language Understanding in Aphasia*. Unpublished doctoral dissertation. The Netherlands: University of Nijmegen.

Hari R, Aittoniemi K, Järvinen M-L, Katila T, Varpula T (1980) Auditory evoked transient and sustained magnetic fields of the human brain: localization of neural generators. *Experimental Brain Research*, **40**, 237–240.

Huber W, Weniger D, Poeck K, Willmes K (1980) Der Aachener Aphasie Test. Aufbau und Uberprüfung der Konstruktion. *Nervenarzt*, **51**, 475–482.

Huber W, Poeck K, Willmes K (1984) The Aachen Aphasia Test. *Advances in Neurology*, **42**, 291–303.

ILS (1978) *Interactive Laboratory Systems*. Santa Barbara: Signal Technology.

Jauhiainen T, Nuutila A (1977) Auditory perception of speech and speech sounds in recent recovered cases of aphasia. *Brain and Language*, **4**, 572–579.

Jerger J, Weikers NJ, Sharbrough FW, Jerger S (1969) Bilateral lesions of the temporal lobe: a case study. *Acta Oto-Laryngologica*, Supplement 258, 7–51.

KLATT DH (1979) Speech perception: a model of acoustic-phonetic analysis and lexical access. *Journal of Phonetics*, **7**, 279–312.

KUHL PK (1986) Theoretical contributions of tests on animals to the special-mechanisms debate in speech. *Experimental Biology*, **45**, 233–265.

LAMBERT J, EUSTACHE F, LECHEVALIER B, ROSSA Y, VIADER F (1989) Auditory aphasia with relative sparing of speech perception. *Cortex*, **25**, 71–82.

LEVY J, TREVARTHEN C (1977) Perceptual, semantic and phonetic aspects of elementary language processes in split-brain patients. *Brain*, **100**, 105–118.

LIBERMAN AM, COOPER FS, SHANKWEILER DP, STUDDERT-KENNEDY M (1967) Perception of the speech code. *Psychological Review*, **74**, 431–461.

LIEBERMAN P, BLUMSTEIN SE (1988) *Speech Physiology, Speech Perception and Acoustic Phonetics*. Cambridge: Cambridge University Press.

LISKER L, ABRAMSON AS (1964) A cross-language study of voicing in initial stops: acoustical measurements. *Word*, **20**, 384–422.

LISSAUER H (1890) Ein Fall von Seelenblindheit nebst einem Beitrage zur Theorie derselben. *Archiv für Psychiatrie und Nervenkrankheiten*, **21**, 222–270.

LURIA AR (1970) Pathology of temporal lobe systems and the syndrome of acoustic aphasia. In: *Traumatic Aphasia: Its Syndromes, Psychology and Treatment*. Edited by A. R. Luria. The Hague: Mouton, pp. 104–141.

MAASSEN B, POVEL D-J (1985) The effect of segmental and suprasegmental corrections on the intelligibility of deaf speech. *Journal of the Acoustical Society of America*, **78**, 877–886.

MATSUI T, HIRANO A (1978) *An Atlas of the Human Brain for Computerized Tomography*. Tokyo: Igaku-Shoin.

MEHLER J (1981) The role of syllables in speech processing: infant and adult data. *Philosophical Transactions of the Royal Society of London, B*, **295**, 333–352.

MENDEZ MF, GEEHAN GR (1988) Cortical auditory disorders: clinical and psychoacoustic features. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 1–9.

METZ-LUTZ M-N, DAHL E (1984) Analysis of word comprehension in a case of pure word deafness. *Brain and Language*, **23**, 13–25.

MICELI G (1982) The processing of speech sounds in a patient with cortical auditory disorder. *Neuropsychologia*, **20**, 5–20.

MICELI G, GAINOTTI G, CALTAGIRONE C, MASULLO C (1980) Some aspects of phonological impairment in aphasia. *Brain and Language*, **11**, 159–169.

MICHEL F, PERONNET F (1980) A case of cortical deafness: clinical and electrophysiological data. *Brain and Language*, **10**, 367–377.

MILBERG W, BLUMSTEIN S, DWORETZKY B (1988) Phonological processing and lexical access in aphasia. *Brain and Language*, **34**, 279–293.

MILLER JL, JUSCZYK PW (1989) Seeking the neurobiological bases of speech perception. *Cognition*, **33**, 111–137.

MOTOMURA N, YAMADORI A, MORI E, TAMARU F (1986) Auditory aphasia: analysis of a case with bilateral subcortical lesions. *Brain*, **109**, 379–391.

ORGASS B (1976) Eine Revision des Token Tests: I. Vereinfachung der Auswertung, Itemanalyse und Einführung einer Alterskorrektur. II. Validitätsnachweis: Normierung und Standardisierung. *Diagnostica*, **22**, 70–87, 141.

OSCAR-BERMAN M, ZURIF EB, BLUMSTEIN S (1975) Effects of unilateral brain damage in the processing of speech sounds. *Brain and Language*, **2**, 345–355.

ÖZDAMAR Ö, KRAUS N, CURRY F (1982) Auditory brain stem and middle latency responses in a patient with cortical deafness. *Electroencephalography and Clinical Neurophysiology*, **53**, 224–230.

PARVING A, SALOMON G, ELBERLING C, LARSEN B, LASEN NA (1980) Middle component of the auditory evoked response in bilateral temporal lobe lesions: report on a patient with auditory agnosia. *Scandinavian Audiology*, **9**, 161–167.

PETERSEN MR, BEECHER MD, ZOLOTH SR, MOODY DB, STEBBINS WC (1978) Neural lateralization of species-specific vocalizations by Japanese macaques (*Macaca fuscata*). *Science*, **202**, 324–327.

PISONI DB, LUCE PA (1987) Acoustic-phonetic representations in word recognition. *Cognition*, **25**, 21–52.

Poeck K, Hartje W (1979) Performance of aphasic patients in visual versus auditory presentation of the Token Test: demonstration of a supra-modal deficit. In: *Auditory Comprehension: Clinical and Experimental Studies with the Token Test.* Edited by F. Boller and M. Dennis. New York: Academic Press, pp. 107–113.

Repp BH (1982) Phonetic trading relations and context effects: new experimental evidence for a speech mode of perception. *Psychological Bulletin,* **92,** 81–110.

Repp BH (1984) Categorical perception: issues, methods, findings. In: *Speech and Language: Advances in Basic Research and Practice,* Volume 10. Edited by N. J. Lass. New York: Academic Press, pp. 243–335.

Riedel K, Studdert-Kennedy M (1985) Extending formant transitions may not improve aphasics' perception of stop consonant place of articulation. *Brain and Language,* **24,** 223–232.

Rubens AB, Johnson MG, Speaks C (1978) Location of lesions responsible for the 'paradoxical ipsilateral ear effect' with dichotic listening tests in patients with aphasia due to stroke. *Neurology, New York,* **28,** 396.

Saffran EM, Marin OSM, Yeni-Komshian GH (1976) An analysis of speech perception in word deafness. *Brain and Language,* **3,** 209–228.

Sams M, Hämäläinen M, Antervo A, Kaukoranta E, Reinikainen K, Hari R (1985) Cerebral neuromagnetic responses evoked by short auditory stimuli. *Electroencephalography and Clinical Neurophysiology,* **61,** 254–266.

Scherg M, Cramon D von (1986) Evoked dipole source potentials of the human auditory cortex. *Electroencephalography and Clinical Neurophysiology,* **65,** 344–360.

Scherg M, Cramon D von (1990) Dipole source potentials of the auditory cortex in normal subjects and in patients with temporal lobe lesions. In: *Auditory Evoked Magnetic Fields and Electric Potentials. Advances in Audiology,* Volume 6. Edited by F. Grandori, M. Hoke and G. L. Romani. Basel and London: Karger, pp. 165–193.

Schuster P, Taterka H (1926) Beitrag zur Anatomie und Klinik der reinen Worttaubheit. *Zeitschrift für die Gesamte Neurologie und Psychiatrie,* **105,** 494–538.

Slis IH, Cohen A (1969) On complex regulating the voiced-voiceless distinction. II. *Language and Speech,* **12,** 137–155.

Sparks R, Geschwind N (1968) Dichotic listening in man after section of neocortical commissures. *Cortex,* **4,** 3–16.

Spinnler H, Vignolo LA (1966) Impaired recognition of meaningful sounds in aphasia. *Cortex,* **2,** 337–348.

Stockert TR von (1982) On the structure of word deafness and mechanisms underlying the fluctuation of disturbances of higher cortical functions. *Brain and Language,* **16,** 133–146.

Strange W, Verbrugge RR, Shankweiler DP, Edman TR (1976) Consonant environment specifies vowel identity. *Journal of the Acoustical Society of America,* **60,** 213–224.

Strange W, Edman TR, Jenkins JJ (1979) Acoustic and phonological factors in vowel identification. *Journal of Experimental Psychology: Human Perception and Performance,* **5,** 643–656.

Studdert-Kennedy M, Shankweiler D (1970) Hemispheric specialization for speech perception. *Journal of the Acoustical Society of America,* **48,** 579–594.

Studdert-Kennedy M, Shankweiler D, Pisoni D (1972) Auditory and phonetic processes in speech perception: evidence from a dichotic study. *Cognitive Psychology,* **3,** 455–466.

Summerfield Q (1982) Differences between spectral dependencies in auditory and phonetic temporal processing: relevance to the perception of voicing in initial stops. *Journal of the Acoustical Society of America,* **72,** 51–61.

Swisher L, Hirsh IJ (1972) Brain damage and the ordering of two temporally successive stimuli. *Neuropsychologia,* **10,** 137–152.

Tallal P, Newcombe F (1978) Impairment of auditory perception and language comprehension in dysphasia. *Brain and Language,* **5,** 13–24.

Tanaka Y, Yamadori A, Mori E (1987) Pure word deafness following bilateral lesions: a psychophysical analysis. *Brain,* **110,** 381–403.

Tartter VC (1988) Acoustic and phonetic feature effects in dichotic listening. In: *Handbook of Dichotic Listening: Theory, Methods and Research.* Edited by K. Hugdahl. Chichester: John Wiley, pp. 283–321.

VARNEY NR (1984) Phonemic imperception in aphasia. *Brain and Language*, **21**, 85–94.

VARNEY NR, BENTON AL (1979) Phonemic discrimination and aural comprehension among aphasic patients. *Journal of Clinical Neuropsychology*, **1**, 65–73.

VIGNOLO LA (1969) Auditory agnosia: a review and report of recent evidence. In: *Contributions to Clinical Neuropsychology*. Edited by A. L. Benton. Chicago: Aldine, pp. 172–208.

WENIGER D, WILLMES K, HUBER W, POECK K (1981) Der Aachener Aphasie Test. Reliabilität und Auswertungsobjektivität. *Nervenarzt*, **52**, 269–277.

WILLMES K, POECK K, WENIGER D, HUBER W (1980) Der Aachener Aphasie Test. Differentielle Validität. *Nervenarzt*, **51**, 553–560.

WILLMES K, POECK K, WENIGER D, HUBER W (1983) Facet theory applied to the construction and validation of the Aachen Aphasia Test *Brain and Language*, **18**, 259–276.

WOODS DL, KNIGHT RT, NEVILLE HJ (1984) Bitemporal lesions dissociate auditory evoked potentials and perception. *Electroencephalography and Clinical Neurophysiology*, **57**, 208–220.

WOODS DL, CLAYWORTH CC, KNIGHT RT, SIMPSON GV, NAESER MA (1987) Generator of middle- and long-latency auditory evoked potentials: implications from studies of patients with bitemporal lesions. *Electroencephalography and Clinical Neurophysiology*, **68**, 132–148.

YAQUB BA, GASCON GG, AL-NOSHA M, WHITAKER H (1988) Pure word deafness (acquired verbal auditory agnosia) in an arabic speaking patient. *Brain*, **111**, 457–466.

YENI-KOMSHIAN GH, LAFONTAINE L (1983) Discrimination and identification of voicing and place contrasts in aphasic patients. *Canadian Journal of Psychology*, **37**, 107–131.

ZAIDEL E (1976) Auditory vocabulary of the right hemisphere following brain bisection or hemidecortication. *Cortex*, **12**, 191–211.

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Brain (1991), **114**, 1227–1244

FREE AND SUPPORTED STANCE IN PARKINSON'S DISEASE

THE EFFECT OF POSTURE AND 'POSTURAL SET' ON LEG MUSCLE RESPONSES TO PERTURBATION, AND ITS RELATION TO THE SEVERITY OF THE DISEASE

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SUMMARY

Upright stance and its reflex control were studied in parkinsonian patients and in age-matched normal subjects. They stood unperturbed on a force-measuring surface (static conditions), or were displaced by movement of a supporting platform (dynamic conditions). During quiet stance the following variables were analysed, with eyes open or closed: position of the centre of foot pressure (CFP), average sway area, length of sway path, amplitude and distribution of tonic leg muscle EMG activity. Perturbations of stance were induced by toe-up or toe-down rotations, and by backward or forward translations of the platform. Amplitude of short, medium and long-latency EMG responses to displacement were measured in the tibialis anterior (TA) and in the three heads of the triceps surae (TS) muscle. The perturbations were produced during both free and supported stance (holding onto a stable structure), under which condition normal subjects suppress medium and long-latency responses.

Under static conditions, the only significant finding in parkinsonians was represented by a shift in the position of the CFP. This was correlated with the severity of the disease (Webster scale), the less affected patients being shifted backwards and the more affected patients forwards, with respect to normals.

Under dynamic conditions, the reflex responses to perturbations of free stance were similar in both groups. Only the medium-latency burst of gastrocnemius lateralis and the long-latency burst TA evoked by TS stretch were larger in parkinsonians. The amplitude of these responses, as well as of all the others, was not related to the Webster score. Within the patients' group, a relationship between position of CFP and area of EMG burst was found for both medium and long-latency TA responses evoked by forward translation and toe-up rotation, respectively.

Under supported conditions, the capability to suppress all medium and long-latency muscle responses to any perturbation was lost or impaired in the parkinsonians. The degree of impairment was unrelated to the position of the CFP, but was significantly related to the severity of the disease. The suppression to 40% (supported/nonsupported), of TA response to toe-down rotation is proposed as the point of separation between normals and parkinsonians.

The forward projection of the CFP, occurring in the severe stages of the disease, and the increase in amplitude of some responses to perturbations of free stance might be a compensatory adaptation to the anomalous upright posture. The inappropriate reduction of the late responses during supported stance is considered as a sign of failure of motor program selection, possibly connected with a disorder of the supplementary motor area.

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INTRODUCTION

Objective methods for quantifying the capability of maintaining body equilibrium, both during quiet stance (Mauritz *et al.*, 1979) and during induced perturbations (Nashner, 1983), have recently been developed. As a consequence, postural deficits specific for the type of the disease have been assessed in various motor disorders (Diener and Dichgans, 1988).

Unexpectedly, parkinsonian patients show only minor disturbances when subjected to this type of examination. Sway oscillations are similar to those of normal subjects, and leg muscle reflex responses to perturbations of stance show latencies in the normal range (Dichgans *et al.*, 1985). Alterations in the amplitude of some EMG responses have been reported, but the various findings seem contradictory. Both increase (Scholz *et al.*, 1987) and decrease in the amplitude of triceps surae responses have been described (Dietz *et al.*, 1988) suggesting that major changes in reflex control of posture are absent in parkinsonian subjects.

The above findings do not equate well with the common disorders observed on clinical examination, such as leaning and an increased likelihood of falls. Thus reflex control of posture per se may well be normal in parkinsonians, but change of posture when needed (Martin, 1965), or interaction of voluntary movement with posture may be affected. Anticipatory adjustments in postural muscles, associated with arm movements, for example, can be defective in standing parkinsonians (Bazalgette *et al.*, 1986; Rogers *et al.*, 1987). Others have shown that parkinsonians do not necessarily fail to exhibit any anticipatory postural response (Dick *et al.*, 1986), but that the response is not an appropriate one (Sanes and Evarts, 1985). Recently, impairment of the coordination between voluntary movement of one arm and activity in the other 'postural' arm has been detected during a bimanual load-lifting task (Viallet *et al.*, 1987).

Taken together, these findings can be interpreted as a sign of failure of appropriate motor program selection in Parkinson's disease, possibly due to a defect of the 'medial' motor system, which includes the supplementary motor area (SMA) and its output (Massion *et al.*, 1989). The increased dependence on visual information reaching the premotor area for successful completion of a variety of voluntary movements is in favour of this hypothesis (*see* Marsden, 1989). It may be of some relevance that, in the monkey, SMA neurons are activated by instructions that determine the response to forthcoming signals, be it initiation or suppression of motor activity (Tanji and Kurata, 1985).

Since it is known that some responses to perturbation in the leg muscles in standing normal subjects are suppressed by changes in the postural 'set' (Nardone *et al.*, 1990*a, b*), we studied parkinsonian patients, affected by the disease to a differing extent, under different postural conditions. During quiet stance, various sway variables were measured with eyes open or closed; during perturbations induced by displacement of the platform, leg muscle responses during free stance were compared with those obtained under supported stance (holding onto a frame). Some of the results have been presented in abstract form (Nardone *et al.*, 1989).

METHODS

Data were collected from 31 patients with idiopathic Parkinson's disease, aged 67.7 (SD ± 7.2, range 55–82) yrs, and 25 control subjects with no history of neurological disease, aged 62.3 ± 8.1 (range 42–76) yrs.

The experimental procedure was approved by the local ethical committee and informed consent was obtained from all subjects. The severity of Parkinson's disease was assessed by means of the Webster rating scale. Table 1 summarizes the clinical features of the patients admitted to the study, all of whom were able to stand and walk without aid. All subjects were tested in a one-day session.

The static condition test was performed by asking the subject to stand as still as possible on an outline drawn at the centre of a dynamometric platform (Kistler type 9281B, Switzerland). The subjects stood both with eyes closed (EC) and open (EO), when they gazed at a target placed at 50 cm, at eye height. Two trials, each one lasting 51 s, were performed under both visual conditions. After each trial the subjects were allowed to sit in order to avoid exhaustion. Only the best performance was considered for further analysis.

The three components of the force acting on the platform were converted analog-to-digital (sampling rate 10 Hz) and fed into an Apple II computer. A program calculated the changes in position of the resultant vector, from which the average centre of foot pressure (CFP) was obtained. The following variables were thus measured: (1) RMSx and RMSy, i.e., the root mean square of the shifts in the CFP along the laterolateral (x axis) and anteroposterior (y axis) direction; (2) SP, the sway path travelled by the CFP during the trial; (3) Area, the surface comprised by the shifts of the CFP; (4) CFPx and CFPy, the average position of the CFP along the x and y axes (*see* Mauritz *et al.*, 1979). The mean CFPy, obtained by averaging the EO data for all normal subjects, was assumed as the origin of the coordinates for further comparison of the EC data of the normals and of both the EO and EC data of the parkinsonians.

During the dynamic condition test, all subjects stood at ease on a movable hydraulic platform (Lomazzi, Italy) with their eyes open Platform rotations (3 deg) were induced in toe-up (upward tilt, UT) or toe-down (downward tilt, DT) direction, around an axis parallel to a line passing through the ankle joints. For 25 patients and for all normals, these perturbations were intermingled at random with backward (BT) and forward (FT) horizontal translations (3 cm). The velocity of platform movement was 50 deg$\cdot$s^{-1} or 50 cm$\cdot$s^{-1}, respectively. Ten trials were performed in every subject for each type of perturbation. The interval between trials varied randomly between 20 and 30 s. The same platform movements were also induced while holding onto a horizontal stable frame (a solid bar) positioned in front of the subjects, who were asked not to grasp the frame forcibly. In 2 patients and 2 normal subjects, recording from the ventral and dorsal aspect of the forearm did not show EMG activity before the perturbations. It was systematically checked by visual inspection that the tibiotarsal, knee and hip angles did not appreciably change under the two conditions. This was confirmed in 3 patients, in whom the change in the initial position of the body segment due to the holding was measured by means of an optoelectronic device (CoSTEL, Log.In, Italy), as described in a previous paper (Nardone *et al.*, 1990*a*): the changes in ankle and knee angles never exceeded two degrees.

The EMGs of soleus (Sol), gastrocnemius medialis (GM), lateralis (GL) and tibialis anterior (TA) of one leg were recorded through bipolar electrodes containing integrated differential amplifiers (×2000) (D.E.M., Italy). The leads consisted of silver/silver-chloride wires 1 cm in length, the distance between leads being 1 cm. This assured maximal selectivity of recording and minimal cross-talk between muscles. The electrodes were positioned on the lower third of the leg, posteriorly (Sol), and on the upper third on the bellies of GM, GL and TA. Signals were band-pass filtered (30–500 Hz), postamplified (×5), A/D converted (sampling rate 1 kHz) and fed to the computer, together with the platform position signal. The period of acquisition lasted 400 ms. The EMG signals were rectified, integrated (time constant 10 ms) and averaged. The time-course of EMG activity was measured on the averaged signal by means of a cursor on the computer screen (1 pixel = 1 ms), and was referred to the onset of platform movement. The onset of each response was defined as the first rising front of the EMG burst leading to a clearly defined peak of activity; the responses lasted until the activity fell again below the voltage corresponding to the onset latency. In the case of the long-latency responses, a window was chosen which lasted up to 80 ms from their onset. The area of the EMG envelope was then computed.

RESULTS

Static conditions

Table 2 gives the average value (±SD) of the variables analysed in parkinsonians and normals during quiet stance. In parkinsonians, the average deviations from the vertical

TABLE 1. SUMMARY OF CLINICAL FEATURES OF THE PARKINSONIAN PATIENTS

Case	*Age (yrs)*	*Sex*	*Duration of illness (yrs)*	*Treatment** *Drug*	*mg/day*	*Webster score*	*Bradykinesia*	*Rigidity*	*Tremor*	*Stooped posture*
1	74	M	14	LDI	675	11	2	2	0	2
				Dep	10					
				Brc	12					
2	68	F	2	Tri	4	7	1	1	2	1
3	61	F	0.5	LDI	375	5	1	1	1	0
				Dep	5					
4	55	F	5	Tri	4	6	1	1	1	0
				Dep	10					
5	82	M	4	LDI	375	7	2	1	0	1
6	61	M	4	LDI	750	8	1	2	1	1
7	74	M	3	LDI	750	15	2	2	1	2
				Dep	5					
8	60	M	2	LDI	375	4	0	1	1	0
9	65	M	7	LDI	250	17	2	2	1	2
10	64	F	1	LDI	125	5	1	1	0	0
				Dep	5					
11	55	F	17	LDI	937	9	1	2	1	0
				Brc	9					
12	68	F	12	LDI	500	5	0	0	2	0
13	58	F	1.5	LDI	125	15	2	2	1	2
14	68	F	11	LDI	250	18	2	2	0	1
				Dep	10					
				Brc	12					
15	66	M	3	LDI	187	8	1	1	0	1
16	76	F	6	LDI	375	10	2	1	0	1
				Tri	6					
				Bip	2					
17	76	M	10	LDI	750	20	2	2	0	2
				Dep	10					
18	65	M	5	LDI	250	10	1	2	0	1
19	76	M	15	LDI	1062	9	1	1	0	1
				Bip	8					
20	76	F	9	LDI	1250	10	2	2	0	1
				Bip	6					
21	74	F	6	Tri	2	11	2	2	1	1
				Ama	100					
22	69	M	16	LDI	562	8	2	1	0	1
				Dep	10					
23	68	F	13	LDI	312	14	2	2	0	2
				Brc	7					
				Tri	4					
24	60	F	6	LDI	312	6	1	1	0	1
				Brc	20					
				Bip	2					
25	72	F	10	LDI	437	12	1	2	2	2
				Dep	10					
26	75	F	0.5	—	—	4	0	1	0	1
27	56	F	11	LDI	625	20	2	2	2	3
				Bip	6					
28	69	F	5	LDI	208	9	2	1	0	1
29	76	F	5	LDI	375	8	1	1	0	1
30	67	F	10	LDI	750	20	3	3	0	3
31	64	F	12	LDI	375	12	2	2	1	2
				Dep	5					

* LDI = levodopa plus dopa-decarboxylase inhibitors; Dep = deprenyl; Brc = bromocriptine; Tri = trihexyphenidyl; Bip = biperidin; Ama = amantadine.

TABLE 2 SWAY VARIABLES DURING QUIET STANCE (MEANS ± SD FROM ALL SUBJECTS)

		Normals		*Parkinsonians*	
		EO	*EC*	*EO*	*EC*
RMSx	mm	2.4±1.8	2.8±1.6	2.0±0.9	2.5±1.5
RMSy	mm	3.6±1.1	5.1±2.4	3.8±1.5	4.6±1.8
SP	mm	372±68	595±196	492±213	697±400
Area	mm^2	857±358	1717±958	1105±663	1865±1422
CFPy	mm	0.0±14.8	−3.8±9.2	−9.9±15.5	−11.4±17.4

EO = eyes open, EC = eyes closed

projection of the centre of gravity (RMSx and RMSy) and the length of the curve that the centre of foot pressure (CFP) describes during the trial (sway path, SP) were also within normal limits, both with eyes open (EO) and closed (EC). The area of the surface comprised within the above curve was larger in parkinsonians than in normals (both EO and EC), but the difference was not significant.

While no difference was found in the mean lateral position of the CFP, a significant difference was found in its mean anteroposterior position (CFPy), which was shifted backwards in parkinsonians by 9.9 mm (EO) and 11.4 mm (EC) with respect to normals (EO) (*see* Table 2 and fig. 1, left panel). CFPy was not significantly influenced by the visual condition, both in normals and parkinsonians.

Unexpectedly, the more severe the disease, the less was the backward shift of the CFPy with respect to the position it assumed in normal subjects. In fact, patients having a low Webster score were inclined backwards to a greater extent than those with a high

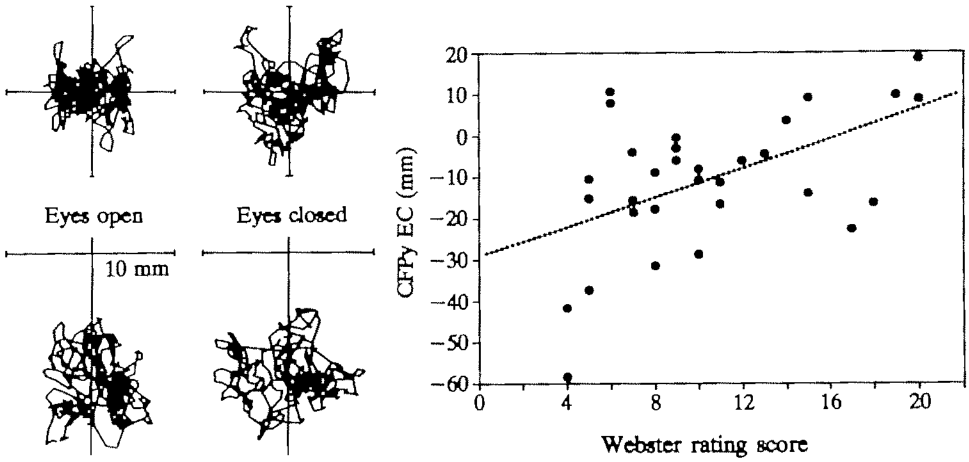

FIG. 1 *Left.* Sway path of the centre of foot pressure (CFP) during eyes open and eyes closed trials performed by a normal subject (*upper panel*) and by a parkinsonian patient (*lower panel*). The CFP is centred on the origin of the axis in the normal subject, under both visual conditions, while it is shifted backwards by about 15 mm in the parkinsonian. Note the similar appearance of the sway path in the 2 subjects. *Right.* Plot of the CFPy (eyes closed, EC) vs the severity of the disease assessed through the Webster scale. It is shown that patients with a low score leant further backwards than patients with higher scores.

score. Along with the increase in the Webster scale, the position of the CFPy showed a trend towards the value found in normals, and even passed beyond it (fig. 1, right panel). The linear regression through the data points was significant, both with EC ($y = -28.9+1.8x$; $P<0.005$, $R^2 = 24.6$) and EO ($P<0.01$, not shown in fig.)

An index of the degree to which each subject relies on visual information for the maintenance of the quiet erect posture is given by the percentage ratio of the area of sway with eyes open to the area of sway with eyes closed (Area EO/Area EC ×100). A value close to 100 would mean that the advantage given by the visual input is negligible, a smaller value would point to a stabilizing effect of vision. The average value of the index was 61.5 ± 30.3 and 73.6 ± 32.0 in normals and parkinsonians, respectively, and the difference was not significant. Furthermore, no regression was found between Area EO/Area EC×100 and either duration or severity of the disease. An EO/EC×100 index was also calculated for the other sway variables, but again no differences between normals and parkinsonians could be found. These results exclude the hypothesis that parkinsonians are inordinately dependent on visual input for the control of postural sway during free stance.

Triceps surae (TS) EMG activity was not significantly different between normals and parkinsonians. No normals showed activity in TA, while 7 parkinsonians had measurable, albeit small and nonconstant activity in this muscle. However, the amplitude of this TA activity, presumably useful for counteracting the posteriorly inclined position, was not correlated significantly either with the position of CFPy or severity of disease.

Dynamic conditions

All perturbations induced a sequence of EMG bursts in the leg muscles. The responses were named on the basis of the latency of onset after platform displacement, according to previous studies (Nardone *et al.*, 1990*a, b*). Short-latency responses (onset around 40 ms) and medium-latency responses (onset between 70 and 100 ms) occurred in the muscle(s) initially stretched by the perturbation. Long-latency responses occurred in the antagonist muscle(s) and were termed antagonist reactions. For the sake of comparison between normals and parkinsonians, measurements have only been performed on those responses which were consistent and presented no identification problems in both groups. Therefore, during TS stretch, the GM and GL SLR, and Sol SLRb (Allum *et al.*, 1988; Huttunen and Hömberg, 1990; Nardone *et al.*, 1990*a, b*), were not measured in either group. During TA stretch only the area of Sol antagonist responses was measured, because these responses in the GM and GL were small and difficult to identify with certainty.

Standing freely

1. *Perturbations stretching the triceps surae*

Upward tilt. The upper part of fig. 2 shows the pattern of EMG responses evoked in the TS and TA muscles by an upward tilt of the platform in a normal subject. The Sol reflex activity was characterized by a large short-latency response followed by a medium-latency response. The responses in GM and GL muscles generally consisted in a small short-latency response followed by a large medium-latency response. The responses in the TS muscle were followed by a well defined antagonist reaction in the TA.

Comparison of the left with the right part of fig. 2 shows that pattern and timing

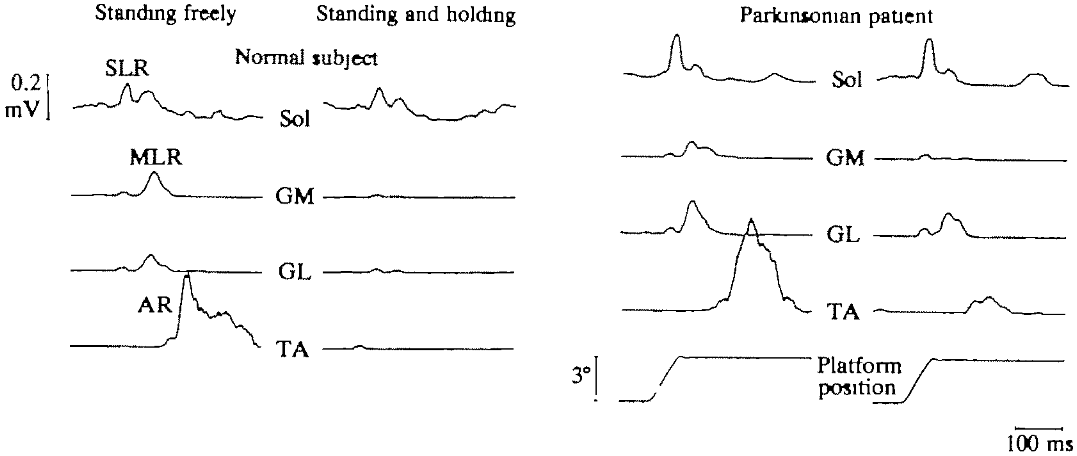

FIG. 2. Rectified and integrated EMG responses (average of 10 trials) of the leg muscles during upward tilt in a normal subject (*left*) and in a parkinsonian patient (*right*), during free stance (*left panels*) and while holding onto a stable frame (*right panels*). Same subjects as in fig. 1. Note the incomplete suppression of GM and GL medium-latency responses (MLRs) and of the TA antagonist response (AR) under supported conditions in the parkinsonian compared with the normal subject. In this and in fig 5, zero level of Sol EMG activity is indicated by the dotted line, for the other muscles it coincides with the flat part of the trace. Sol = soleus; GM = gastrocnemius medialis; GL = gastrocnemius lateralis, TA = tibialis anterior, AR = antagonist response, SLR = short-latency response

of all responses were similar in the two groups. The mean latencies in the normals were compatible with those observed in another group of normal subjects (Nardone *et al.*, 1990*b*); the latencies in parkinsonians were not different from normals, except for the TA antagonist response, considered to be the stabilizing response during upward tilt, whose onset was 18.6 ms longer, on the average ($P < 0.001$). Since differences in the amplitude of medium or long-latency responses to stretch have previously been found by some authors in both the upper (Rothwell *et al.*, 1983; Lee, 1989) and lower limbs (Scholz *et al.*, 1987; Dietz *et al.*, 1988) we compared the area of all the responses studied (fig. 3). Between our two groups, however, a significant difference was found only in the average area of GL medium-latency responses ($P < 0.05$) and TA antagonist reactions ($P < 0.005$), which were larger in parkinsonians. Within the latter group, the area of these responses, as well as of the others, was not significantly correlated either with the disability score or with the degree of rigidity. The TA antagonist reaction was larger in those patients displaying tonic TA activity during stance. A significant correlation existed between the area of the TA antagonist reaction and the position of the CFPy, the response being larger the further backwards the position of CFPy (EO) (fig. 4, right panel: the regression line is $y = 2.85-0.06x$, $P < 0.01$, $R^2 = 24.4$). Such a correlation also held if the parkinsonians displaying TA tonic activity were excluded from analysis.

Backward translation. The timing of the EMG responses induced by backward translation were similar to those described above, and were indistinguishable between normals and parkinsonians. The area of the responses was also not different between the two groups, except for the GL medium-latency response, which was larger

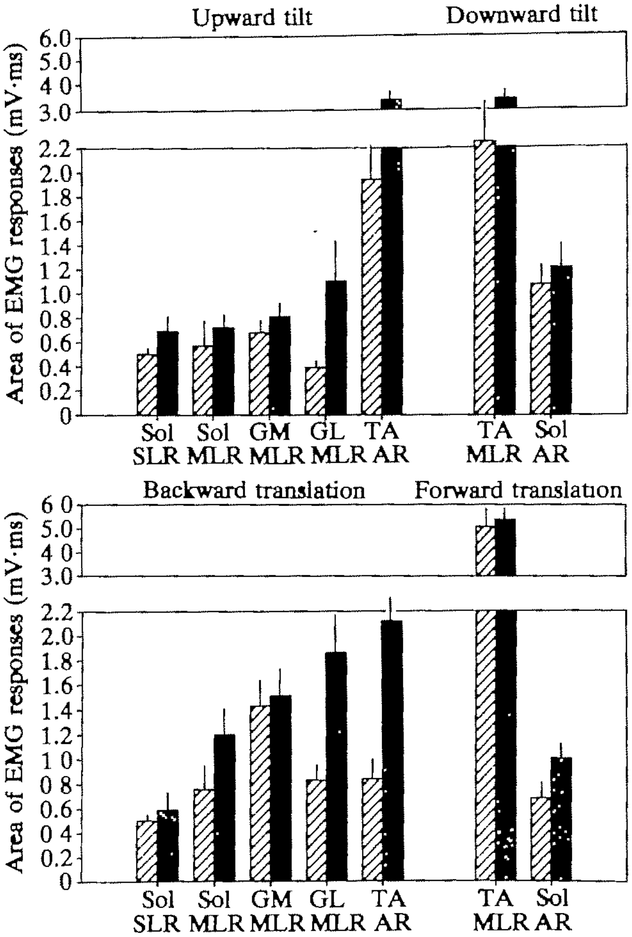

FIG. 3 Area of the leg muscle EMG responses during tilts (*upper panel*) and translations (*lower panel*) under freely standing conditions. Each bar is the average (± SEM) of the data from all normals (left-sided bars) and all parkinsonians (right-sided bars) A statistically significant difference in the area of the responses between normals and parkinsonians is present only in the case of the GL medium-latency response (MLR) and the TA antagonist reaction (AR) during upward tilt and backward translation. For abbreviations, *see* fig 2.

($P < 0.02$), and for the TA antagonist reaction, which was more than double in parkinsonians than in normals ($P < 0.001$) (fig. 3, lower left histograms). The TA antagonist reaction was not influenced by TA tonic activity. No correlation was found between the area of either medium-latency responses or antagonist reactions and the Webster score or CFPy.

Differences between UT and BT-evoked responses. In both the normal subjects and the parkinsonian patients the mean area of GM and GL medium-latency responses was larger, whereas the mean area of the TA antagonist reaction was smaller, in backward translation than in upward tilt (fig. 3, left histograms). The finding was not unexpected in

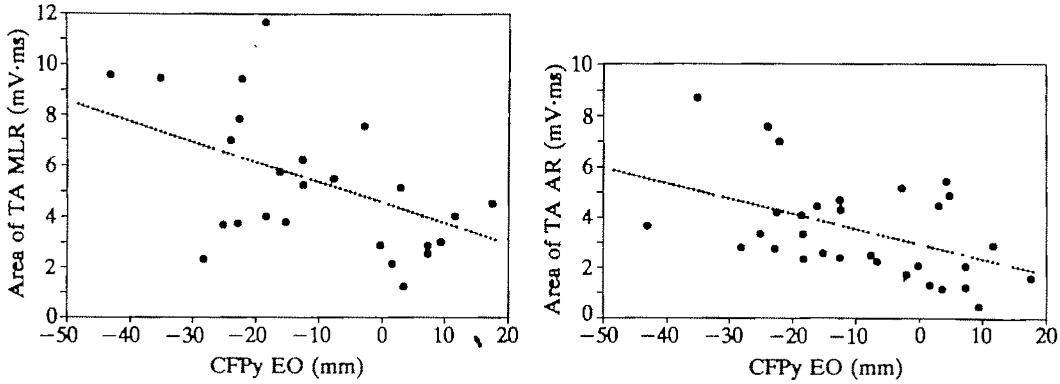

FIG. 4 Relationship between area of TA responses and position of the centre of foot pressure (CFPy) in the parkinsonians. The amplitude of both the TA medium-latency response (MLR) evoked by forward translation (*left panel*) and the TA antagonist response (AR) evoked by upward tilt (*right panel*) was large in the patients having a backward shift of the position of the CFPy, and was small in those leaning forwards.

normals, since the effect of the perturbation type (rotation vs translation) had been reported previously for the GM responses (Hansen *et al.*, 1988) and also for other responses (Nardone *et al.*, 1990*b*). It is now clear that the amplitude of the responses depends on the type of perturbation in parkinsonians as well.

2. *Perturbations stretching the tibialis anterior*

Downward tilt. The EMG activity induced by downward tilt consisted in a large medium-latency response in the TA, followed by antagonist reactions in TS (fig. 5), generally larger in Sol than in GM and GL. The pattern and latency of the responses were similar in both normals and parkinsonians. In particular, the mean area of the TA medium-latency response and Sol antagonist reaction was not significantly different between the two groups, even if an indication was present that the TA medium-latency response was larger in parkinsonians (fig. 3, upper right histograms). In the patients, the amplitude of the TA medium-latency response was not influenced by the level of background activity in the TA muscle, and was not correlated with CFPy or the Webster score.

Forward translation. Latency and area of the responses to forward translation were not significantly different between the two groups. In the patients, the area of the TA medium-latency response was larger the further backwards was the position of the CFPy (fig. 4, left panel) ($y = 4.28-0.1x$, $P < 0.01$, $R^2 = 27.3$), while it was not influenced by the level of TA tonic activity or the Webster score. In both groups the area of the TA medium-latency response was larger, while that of Sol antagonist reaction was smaller, during forward translation than downward tilt (fig. 3, right histograms).

Supported postural conditions: standing and holding

The responses of the leg muscles to the four types of perturbation were also recorded during stabilized posture, while the subjects held onto a stable frame positioned in front of them. On average, the background EMG activity of Sol, GM and GL decreased to

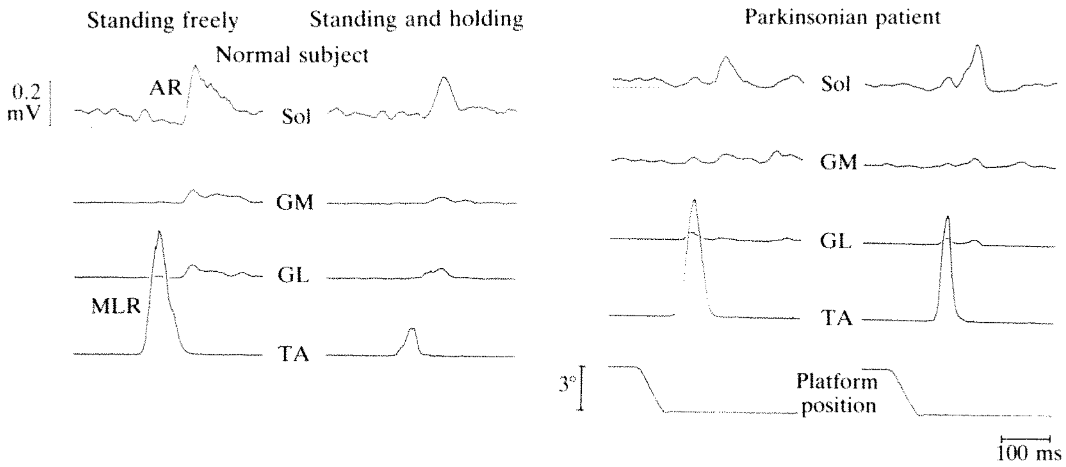

FIG. 5. Rectified and integrated EMG responses of the leg muscles during downward tilt in a normal subject (*left*) and in a parkinsonian patient (*right*) during free stance (left panels) and while holding onto a frame (right panels). Same subjects as in fig. 1. Note the almost absent suppression of the TA medium-latency response (MLR) under supported conditions in the parkinsonian compared with the normal. On the contrary, the Sol antagonist reaction (AR) is little influenced by the postural set in either subject. For abbreviations, *see* fig. 2.

about two-thirds of that present under free stance, both in normals and parkinsonians. The limited tonic EMG activity of TA, present in 7 patients under the standing freely condition, disappeared in 4 and decreased in 3.

The consequence of the supported condition on some of the leg muscle responses was strikingly different between normals and parkinsonians. In normals, during upward tilt (fig. 2) and backward translation, the GM and GL medium-latency responses and the TA antagonist reactions were markedly reduced or completely abolished, the Sol medium-latency responses were little affected, while all short-latency responses were not affected. In the parkinsonians, holding once more induced no changes in the area of the short-latency responses evoked either by upward tilt or backward translation, but the later responses that were diminished in normals were reduced to a much lesser extent. Also during downward tilt (fig. 5) and forward translation, the large TA medium-latency responses were strikingly reduced in the normals, while they were influenced to a much lesser extent in the parkinsonians. Out of the latter group, the 7 patients who showed tonic TA activity during free stance (both the 4 in which EMG disappeared when stabilized and the 3 in which it decreased) suppressed the TA medium-latency response to the same extent as the remaining patients, on the average.

The graph of fig. 6 plots the average percentage value of the area of the various responses observed under supported conditions with respect to standing freely, in both normals and parkinsonians during rotations (upper panel) and translations (lower panel). It is shown that all the responses, except those for Sol, were significantly more influenced by the support in normals than in parkinsonians.

Relationship between degree of response suppression and severity of the disease

Not all patients showed the same impairment in modulating the EMG responses. Some of them, among those less affected by the disease, showed a decrease of the responses

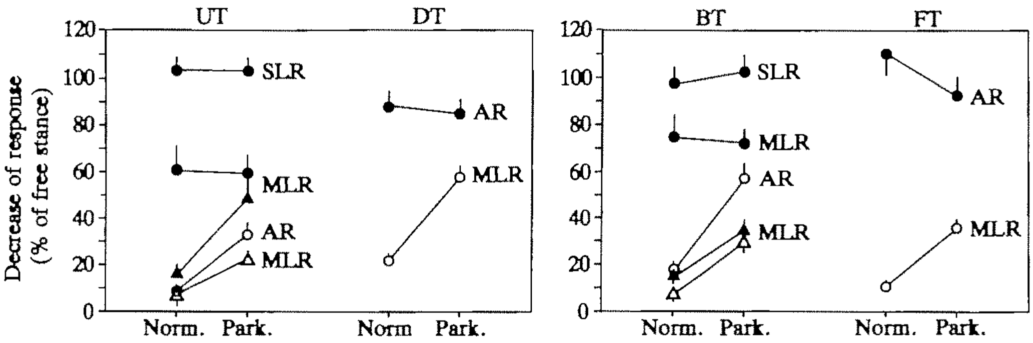

FIG 6. Effect of holding onto a frame on the area of the EMG responses shown in fig. 3, during tilts (*left panel*) and translations (*right panel*). The area under supported conditions is expressed as percentage of the corresponding value during free stance. Each symbol indicates the average value (±SEM) of the amplitude of the various muscles' responses, in all normals and parkinsonians. Filled circles = Sol; open circles = TA; filled triangles = GM, open triangles = GL. UT = upward tilt; DT = downward tilt, BT = backward translation; FT = forward translation.

similar to that occurring in normals. Fig. 7 (left panel) shows that a significant regression existed between the decrease of the TA medium-latency response, evoked by downward tilt under holding conditions, and the severity of the disease assessed through the Webster rating scale ($y = 21.2+3.6x$, $P < 0.002$, $R^2 = 39.2$). Such a regression was significant also in the TA medium-latency response evoked by forward translation ($y = 10.3+2.4x$, $P < 0.01$, $R^2 = 27.8$, not shown in fig.). The percentage suppression induced by holding was not correlated with the disability scores for other responses to the same or to other types of perturbations.

The percentage suppression of the TA medium-latency response during downward tilt in parkinsonians was correlated neither with age nor with duration of the disease.

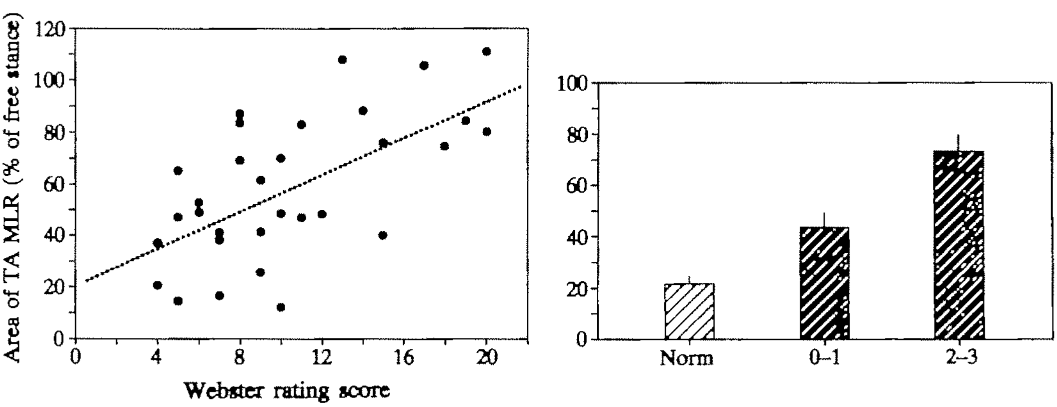

FIG. 7. Relationship between suppression of TA medium-latency response (MLR) to downward tilt and severity of the disease (*left panel*) and rigidity (*right panel*). EMG area under supported conditions is expressed as a percentage of the corresponding value during free stance. The more severe the disease the lesser was the suppression of the response while holding onto a frame. In the lower panel the different degrees of suppression are compared between normals and patients with low (0−1) and high (2−3) rigidity score.

In particular, it was not correlated with the position of the CFPy during unperturbed stance. Further, no significant correlation was found between the ability to suppress the responses and bradykinesia, tremor, and medication. However, a significant regression was found between suppression of the TA medium-latency response in downward tilt and rigidity ($y = 21.3+26.6x$, $P < 0.006$, $R^2 = 23$, not shown). Fig. 7 (right panel) compares the degree of suppression in the normals with those in two groups of parkinsonians having low ($0-1$, $n = 15$) or high ($2-3$, $n = 16$) Webster scores for rigidity. The means of the three groups were significantly different ($P < 0.001$).

Because of the above result, we recalculated the regression between percentage suppression of the TA medium-latency response during downward tilt and the Webster score, after elimination from the latter of the contribution of rigidity. Notably, the slope remained significant ($y = 23.4+4x$, $P < 0.0002$, $R^2 = 39.0$). This means that the defect leading to rigidity, or rigidity itself, are not only cause of the altered suppression. Instead, the latter might be traced to the basic pathophysiological mechanism responsible for the whole parkinsonian motor syndrome. An alternative possibility would be that rigidity is included in other items of the Webster score.

Separation between normals and parkinsonians

The frequency histogram of fig. 8 (left panel) shows the distribution of the area of the TA medium-latency response evoked by downward tilt in normals and parkinsonians, as a percentage of the area under free-stance. All normals decreased the response to less than 40%, whereas most parkinsonian patients decreased the response to a lesser extent. Only 7 of them fell within normal limits; these had a Webster score (6.6 ± 2.4) significantly lower than that of the remaining ones (11.5 ± 4.8). A graph was also drawn for the other responses (including the TA medium-latency response evoked by forward translation), but the TA medium-latency response during downward tilt allowed the most precise discrimination between normals and parkinsonians, owing to the minimum overlap between the two histograms. In particular, the two normal distribution curves fitted to the data meet on the abscissa in correspondence to 40%, which is exactly the upper limit of suppression in our group of normal subjects (fig. 8, right panel).

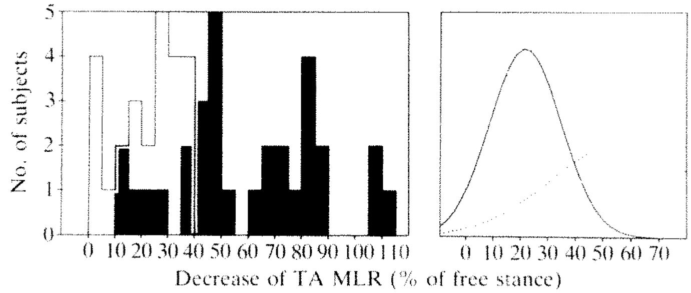

FIG. 8. Distribution of the subjects and patients according to the degree of suppression of TA medium-latency response (MLR) during downward tilt. *Left panel:* frequency histogram of the area of TA MLR under supported conditions, expressed as a percentage of the value during free stance, in normals (open bars) and in parkinsonians (filled bars). All normals reduced the response to below 40%, while most of the parkinsonians were unable to decrease the response to below this level. *Right panel:* normal distribution curves fitted to the two sets of data (normals: 21.8 ± 13.1, continuous line; parkinsonians: 58.9 ± 27.8, dotted line) intersect at 40% on the abscissa.

DISCUSSION

Quiet upright stance

The results show that the mechanisms maintaining stance are not severely disrupted in parkinsonians. In fact, the area of body sway was not significantly larger when compared with normals, and this was true both with eyes open and closed. Other investigations have shown no specific sway pattern in Parkinson's disease (Gregoric and Lavric, 1977; Dichgans *et al.*, 1985), in spite of the altered body posture.

However, the average centre of foot pressure (CFP), which under static conditions approximates the projection of the centre of body mass (Panzer and Hallett, 1988), could be shifted in the anteroposterior direction (y axis) to a varied extent in the patients with respect to normals. The more severely affected patients were liable to be shifted forwards, while a large backward shift was present in those with a low Webster scoring. This unexpected finding raises the possibility that significant changes in the projection of the CFPy are already present by the time the diagnosis is made. The paradoxical return towards and beyond normal values for the patients having a high Webster score might be connected with the flexed attitude that they are compelled to assume in compensation for their backward thrust. This posture would develop regardless or in spite of deterioration in the disease, and might be triggered on reaching a critical point in disease progression and/or in the equilibrium itself. The association of the backward shift of the CFPy with low Webster scores identifies the former as an early marker of parkinsonism.

Responses to perturbations

When the equilibrium of the parkinsonians was perturbed by the displacement of the platform, at least at the velocity used here, the short-latency and most of the medium and long-latency reflex responses of the leg muscles were indistinguishable from those of the normals. The only differing figures were the increased latency of the TA antagonist reaction induced by upward tilt and the increased amplitude of the GL medium-latency response and of the TA antagonist reaction induced by both upward tilt and backward translation.

Our results agree with most of the previous investigations, showing no changes in either latency or amplitude for most of the leg muscle responses in parkinsonians (Chan *et al.*, 1979; Scholz *et al.*, 1987; Dietz *et al.*, 1988). Minor changes in latency for the TA antagonist reaction during upward tilt, compatible with the delay of about 20 ms reported here, were shown by Allum *et al.* (1988) and Scholz *et al.* (1987). Dichgans *et al.* (1985) and Scholz *et al.* (1987) considered the increased amplitude of TS medium-latency response during upward tilt characteristic of Parkinson's disease. That finding is not contradictory, since their bipolar recording from the whole TS would be influenced, and possibly to a major extent, by the GL muscle activity (*see* Methods in Diener *et al.*, 1984); also in our hands the GL medium-latency response showed a significant increase in parkinsonians.

A significant difference between parkinsonians and normals was present in the mean area of the antagonist reactions of the TA occurring when the TS is stretched (both upward tilt and backward translation). This result is in accordance with the findings of Dietz *et al.* (1988). Scholz *et al.* (1987) also described an increase in TA antagonist reaction, albeit nonsignificant. The TA antagonist reactions might be larger in the patients because they occur in response to perturbations shortening the TA muscle, therefore capable of evoking a TA shortening reaction, known to be exaggerated in Parkinson's disease (Diener *et al.*, 1987). However, the larger magnitude of the TA antagonist reactions might also be an expression of a learned postural adaptation to altered biomechanical situations such as an increased likelihood of falling backwards (Allum *et al.*, 1988) or change in muscle stiffness (Dietz *et al.*, 1988). In this way we would interpret the significant regression between the amplitude of the TA antagonist reaction evoked by upward tilt and the position of the CFPy: the further backwards is the body, the more useful becomes this TA response, because it is the stabilizing response during the toe-up rotation. The regression holds both for all the patients, and for the two subgroups with or without TA activity during stance.

In this connection, it is remarkable that a significant regression with the CFPy was also found for the area of TA medium-latency reaction under the forward translation condition, that is, when this response is stabilizing. On the other hand, the TA medium-latency response during downward tilt and TA antagonist response during backward tilt which are not stabilizing, were not correlated with the CFPy. These facts favour the notion that the increased amplitude of some of the leg muscle reflex responses in the patients is not necessarily connected to increased motoneuronal excitability but to the posture they assume (fig. 4) (*see* Diener *et al.*, 1983).

Effects of postural set

The unchanged amplitude of the short and of most medium-latency responses to perturbation of free stance in parkinsonians suggests that changes in excitability of the pathways travelled by impulses originating in the muscle spindles (Berardelli *et al.*, 1983; Cody *et al.*, 1986) do not occur or play a minor role. Instead, changes in the postural 'set', such as holding onto a frame in contrast to standing freely, clearly failed to influence the responses to perturbations to the same extent as in normals.

In normals, the stabilized condition did not influence the short-latency responses, but markedly decreased the amplitude of the medium-latency responses of the stretched muscles and of the later antagonist reactions. Also in parkinsonians the short-latency responses were not affected by the postural set, but the medium-latency responses and the antagonist reactions decreased to a lesser extent than in normals. The persistence of these responses, when they would be of no use, points to an inability to modulate the gain of the responsible pathways depending on the constraints of the postural tasks. This is most likely due to a disturbed supraspinal control for the following reasons. (1) Any remaining tonic activity in the TA during holding, reflecting an increased excitability of the alpha motoneurons, did not necessarily cause a special impairment in the suppression of the responses. (2) Under the standing freely condition, the response of both the stretched muscles and of the antagonists did undergo changes in amplitude dependent on the *type* of perturbation. In fact, both in normals and in parkinsonians the medium-latency responses were larger during horizontal platform translations than during upward or downward rotations; such an effect was attributed in normals to a different input to the spinal cord connected to the activation of different receptors by the two types of perturbation (Nardone *et al.*, 1990*a*).

The absent or reduced modulation of stretch-evoked responses in parkinsonians under supported conditions may have various explanations. (1) Some descending control on the interneurons interposed along the excitatory group II pathway might be defective, increasing with disease severity. The interneurons would in fact be inhibited in normals to avoid the release of reflex activity under circumstances (stabilized posture) in which it would not be useful (Cody *et al.*, 1986). A disordered SMA could be the cause of this deficit, since the SMA is known to project to, among other targets, the spinal intermediate zone (Cheema *et al.*, 1983; Hummelsheim *et al.*, 1986). (2) Gamma motoneurons could escape descending modulation (Andrews *et al.*, 1972): the gamma drive would be equal in normals and parkinsonians during free stance, and would decrease to a greater extent in normals than in parkinsonians under supported conditions, along with the decrease in alpha activity.

In this view, the free stance condition would be the 'standard' state, when the spinal reflex excitability and/or the gamma activity are set at their maximum value. The normality of most responses to perturbation in free standing parkinsonians is in favour of this hypothesis. The supported stance, instead, would be a regulated state, under which the activity in the descending pathways would be attenuated.

The increased responses to muscle stretch or to electrical stimulation of afferent fibres observed previously in parkinsonians would imply that the experimental paradigm required a stabilized postural set, since it is obviously in this state that the responses differ from normal. In fact, under the conditions of most published investigations, the patients were seated, that is, under a more or less 'supported' set, when the medium latency responses of the arm muscles were investigated (Lee and Tatton, 1978; Mortimer and Webster, 1979; Rothwell *et al.*, 1983; Berardelli *et al.*, 1986; Hunter *et al.*, 1988). The possibility that arm muscles are subjected to a different control, more easily altered in parkinsonians than for leg muscles, cannot be excluded. However, it is noticeable that the antagonist reactions in the TA tested in a group of parkinsonians were not different under seated or standing conditions (Diener *et al.*, 1987), as if sitting does not also decrease the reflex excitability commensurately in the leg muscles. The inability to change the motor output according to 'set' might be characteristic of parkinsonism, since patients with Huntington's disease (Huttunen and Hömberg, 1990) or with postural imbalance due to other motor disorders (unpublished observations) are still able to suppress their EMG responses appropriately.

Usefulness of the posturographic tests

The changes induced by the postural set in the medium-latency responses are not all-or-none, but are variably expressed in parkinsonians as a funtion of the severity of the disease. Suppression by holding the TA medium-latency response evoked by downward tilt to at least 40% of the value observed in free stance has been found in all normal subjects, while only 21% of the patients, having a low Webster score, lay below this value. Since (1) the mean amplitude of the TA medium-latency response during downward tilt is not different in normals and parkinsonians during free stance, and (2) there is no correlation between the area and its suppression by holding, the percentage reduction of the response is free from changes in its absolute amplitude. Further, since no correlation was found between suppression of the TA medium-latency response and the position of the centre of feet pressure, this index is not influenced by a particular postural attitude. In addition, rigidity is not the main responsible factor in determining its value, since the same relationship between suppression and severity can be found if the rigidity scores are subtracted from the total Webster score: thus the index is not sort of 'side effect' of the rigidity itself. A further advantage is that possible artefacts linked to electrode position or impedance, and to the amount of active muscle 'seen' by the electrodes are annulled, since each patient serves as his own control. Therefore, this index can be used repeatedly, and in all types of parkinsonians, in order to monitor the disease progression or the effectiveness of treatment.

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REFERENCES

Allum JHJ, Keshner EA, Honegger F, Wuethrich R (1988) Disturbance of posture in patients with Parkinson's disease. In: *Posture and Gait: Development, Adaptation and Modulation.* Edited by B. Amblard, A. Berthoz and F. Clarac. Amsterdam: Elsevier, pp. 245–257.

Andrews CJ, Burke D, Lance JW (1972) The response to muscle stretch and shortening in parkinsonian rigidity. *Brain,* **95,** 795–812.

Bazalgette D, Zattara M, Bathien N, Bouisset S, Rondot P (1986) Postural adjustments associated with rapid voluntary arm movements in patients with Parkinson's disease. *Advances in Neurology,* **45,** 371–374.

Berardelli A, Sabra AF, Hallett M (1983) Physiological mechanisms of rigidity in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry,* **46,** 45–53.

Berardelli A, Dick JPR, Rothwell JC, Day BL, Marsden CD (1986) Scaling of the size of the first agonist EMG burst during rapid wrist movements in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry,* **49,** 1273–1279.

Chan CWY, Kearney RE, Melvill Jones G (1979) Tibialis anterior response to sudden ankle displacements in normal and parkinsonian subjects. *Brain Research, Amsterdam,* **173,** 303–314.

Cheema SS, Whitsel BL, Rustioni A (1983) Cortico-spinal projections from the pericentral and supplementary cortices in macaques as revealed by anterograde transport of horseradish peroxidase. *Neuroscience Letters,* Supplement 14, S62.

Cody FWJ, MacDermott N, Matthews PBC, Richardson HC (1986) Observations on the genesis of the stretch reflex in Parkinson's disease. *Brain,* **109,** 229–249.

Dichgans J, Diener HC, Muller A (1985) Characteristics of increased postural sway and abnormal long loop responses in patients with cerebellar diseases and parkinsonism. In: *Electromyography and Evoked Potentials: Theories and Applications.* Edited by A. Struppler and A. Weindl. Berlin: Springer, pp. 68–74.

Dick JPR, Rothwell JC, Berardelli A, Thompson PD, Gioux M, Benecke R *et al* (1986) Associated postural adjustment in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry,* **49,** 1378–1385.

Diener HC, Dichgans J (1988) Anwendung und Nutzen der statischen und dynamischen Standmessung (Posturographie). *Fortschritte der Neurologie-Psychiatrie,* **56,** 249–258.

Diener HC, Bootz F, Dichgans J, Bruzek W (1983) Variability of postural 'reflexes' in humans. *Experimental Brain Research,* **52,** 423–428.

Diener HC, Dichgans J, Bootz F, Bacher M (1984) Early stabilization of human posture after a sudden disturbance: influence of rate and amplitude of displacement. *Experimental Brain Research,* **56,** 126–134.

Diener C, Scholz, E, Guschlbauer B, Dichgans J (1987) Increased shortening reaction in Parkinson's disease reflects a difficulty in modulating long loop reflexes. *Movement Disorders*, **2**, 31–36.

Dietz V, Berger W, Horstmann GA (1988) Posture in Parkinson's disease: impairment of reflexes and programming. *Annals of Neurology*, **24**, 660–669.

Gregoric M, Lavric A (1977) Statokinesimetric analysis of the postural control in parkinsonism. *Agressologie*, **18**, Supplement A, 45–48.

Hansen PD, Woollacott MH, Debu B (1988) Postural responses to changing task conditions. *Experimental Brain Research*, **73**, 627–636.

Hummelsheim H, Wiesendanger M, Bianchetti M, Wiesendanger R, MacPherson J (1986) Further investigations of the efferent linkage of the supplementary motor area (SMA) with the spinal cord in the monkey. *Experimental Brain Research*, **65**, 75–82.

Hunter JP, Ashby P, Lang AE (1988) Afferents contributing to the exaggerated long latency reflex response to electrical stimulation in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 1405–1410.

Huttunen J, Homberg V (1990) EMG responses in leg muscles to postural perturbations in Huntington's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **53**, 55–62.

Lee RG (1989) Pathophysiology of rigidity and akinesia in Parkinson's disease. *European Neurology*, **29**, Supplement 1, 13–18.

Lee RG, Tatton WG (1978) Long loop reflexes in man: clinical applications. In: *Cerebral Motor Control in Man: Long Loop Mechanisms. Progress in Clinical Neurophysiology*, Volume 4. Edited by J. E. Desmedt. Basel: S. Karger, pp. 320–333.

Marsden CD (1989) Slowness of movement in Parkinson's disease. *Movement Disorders*, **4**, Supplement 1, S26–S37.

Martin JP (1965) Tilting reactions and disorders of the basal ganglia. *Brain*, **88**, 855–874.

Massion J, Viallet F, Massarino R, Khalil R (1989) La région de l'aire motrice supplémentaire est impliquée dans la coordination entre posture et mouvement chez l'Homme. *Comptes Rendus de L'Academie des Sciences, Paris*, Série III, **308**, 417–423.

Mauritz KH, Dichgans J, Hufschmidt A (1979) Quantitative analysis of stance in late cortical cerebellar atrophy of the anterior lobe and other forms of cerebellar ataxia. *Brain*, **102**, 461–482.

Mortimer JA, Webster DD (1979) Evidence for a quantitative association between EMG stretch responses and parkinsonian rigidity. *Brain Research, Amsterdam*, **162**, 169–173.

Nardone A, Mazzini L, Corrà T, Schieppati M (1989) Postural adjustments in normals and in Parkinsonians. Effect of postural set. *VI International Symposium on Motor Control*. Albena, Bulgaria. No. 129, p. 154.

Nardone A, Giordano A, Corrà T, Schieppati M (1990*a*) Responses of leg muscles in humans displaced while standing: effects of types of perturbation and of postural set. *Brain*, **113**, 65–84.

Nardone A, Corrà T, Schieppati M (1990*b*) Different activations of the soleus and gastrocnemii muscles in response to various types of stance perturbation in man. *Experimental Brain Research*, **80**, 323–332.

Nashner LM (1983) Analysis of movement control in man using the movable platform. *Advances in Neurology*, **39**, 607–619.

Panzer VP, Hallett M (1988) Biomechanical assessment of balance control in Parkinson's disease. *Abstracts, 1988 Congress of the International Medical Society of Motor Disturbances*, p. 48, p. 64.

Rogers MW, Kukulka CG, Soderberg GL (1987) Postural adjustments preceding rapid arm movements in parkinsonian subjects. *Neuroscience Letters*, **75**, 246–251.

Rothwell JC, Obeso JA, Traub MM, Marsden CD (1983) The behaviour of the long-latency stretch reflex in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **46**, 35–44.

Sanes JN, Evarts EV (1985) Psychomotor performance in Parkinson's disease. In· *Clinical Neurophysiology in Parkinsonism: Contribution to Assessment and Pathophysiology*. Edited by P. J. Delwaide and A. Agnoli. Amsterdam: Elsevier, pp. 117–132.

Scholz E, Diener HC, Noth J, Friedemann H, Dichgans J, Bacher M (1987) Medium and long latency EMG responses in leg muscles: Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 66–70.

TANJI J, KURATA K (1985) Contrasting neuronal activity in supplementary and precentral motor cortex of monkeys. I. Responses to instructions determining motor responses to forthcoming signals of different modalities. *Journal of Neurophysiology*, **53**, 129–141

VIALLET F, MASSION J, MASSARINO R, KHALIL R (1987) Performance of a bimanual load-lifting task by parkinsonian patients. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 1274–1283.

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A CLINICOPATHOLOGICAL STUDY OF THE GUILLAIN-BARRÉ SYNDROME

NINE CASES AND LITERATURE REVIEW

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SUMMARY

The postmortem findings are reported from 9 cases of the Guillain-Barré syndrome with survival between 10 days and 1 yr. In 8 cases there was multifocal loss of myelin throughout the peripheral nervous system with relative preservation of axons. In 1 case there was predominant loss of axons. Inflammatory mononuclear cell infiltration was present in the peripheral nervous system of all cases except 1 case surviving a year. The extent and severity of cell infiltration was variable, usually being less prominent than in previous reports, and sometimes sparing nerves in which myelin destruction was severe. Vesicular dissolution of myelin noted by electron microscopy was considered to be a postmortem artefact. In cases examined within 30 days after the onset, immunohistochemical studies with monoclonal antibodies identified more leucocytes (PD7/2B11+) and T cells (UCHL1+) in the endoneurium than in cases examined later or control cases. These findings and recent single case reports indicate that the pathology of the Guillain-Barré syndrome is variable. This variability may reflect differences in pathogenesis, with greater cell-mediated immunity in some cases and greater antibody targeted macrophage-mediated demyelination in others.

INTRODUCTION

Acute ascending paralysis resembling the Guillain-Barré syndrome (GBS) was first described by Landry in 1859 but the pathological basis was poorly understood until the middle of the twentieth century. In 1949 Haymaker and Kernohan reported the histological findings in 50 fatal cases of GBS. They suggested that oedema of the nerves and especially the spinal roots was the first change, followed by swelling and disintegration of myelin, appearance of a few lymphocytes and macrophages, and finally the proliferation of Schwann cells. They considered the inflammatory cells as part of the reparative process and not as mediators of demyelination, since they appeared late in the course of the disease. Two decades later Asbury *et al.* (1969) reported the pathological findings in 19 cases of GBS and emphasized the prominence of lymphocytes which they considered responsible for nerve damage. They did not notice any oedema of the spinal roots. Neither study explained the mechanism for myelin breakdown.

Ultrastructural studies revealed that demyelination proceeded only in the presence of mononuclear cells which penetrated the Schwann cell basement membrane, stripped

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off myelin lamellae and phagocytosed and digested myelin debris (Prineas, 1972, 1981; Brechenmacher *et al.*, 1987). Vesicular dissolution was also considered a prominent mechanism of demyelination on the basis of autopsy studies (Wiśniewski *et al.*, 1969; Carpenter, 1972). However, vesicular dissolution has been considered to be a postmortem artefact because such dissolution is only detected in a small number of fibres in a minority of biopsies (Prineas, 1981; Brechenmacher *et al.*, 1987).

The pathological changes in the peripheral nervous system (PNS) in GBS have been considered similar to those in experimental allergic neuritis (EAN) which can be induced by immunizing animals with peripheral nerve myelin (Waksman and Adams, 1955, 1956; Asbury *et al.*, 1969). Prineas (1972) showed that demyelination in GBS proceeds by the same macrophage-associated mechanism demonstrated in EAN by Lampert (1969). The major antigen responsible for producing EAN is the P_2 protein (Kadlubowski *et al.*, 1980). The histological picture of inflammation and demyelination induced by immunization with P_2 protein closely mimics that produced by myelin (Hughes and Powell, 1984; Rostami *et al.*, 1984). EAN can be transferred by a T helper cell line (Linington *et al.*, 1984) and prevented by adult thymectomy, irradiation and reconstitution with B cells (Brosnan *et al.*, 1987). These observations suggest that EAN is due to a T cell-mediated mechanism but do not explain the final mechanism by which the macrophages are activated and targeted specifically against myelin.

A demyelinating polyradiculoneuropathy has been induced by immunizing rabbits with galactocerebroside, a glycolipid which is a major component of peripheral nervous system and central nervous system (CNS) myelin (Saida *et al.*, 1979, 1981). In this model there is evidence that the mechanism of demyelination is a complement-dependent antibody attack on the Schwann cell or myelin or both (Saida *et al.*, 1981; Powell *et al.*, 1984; Stoll *et al.*, 1986). Although macrophage-associated demyelination is evident in galactocerebroside-induced neuritis in rabbits, lymphocytic infiltration is sparse.

There is a discrepancy in the literature concerning lymphocytic infiltration in the PNS of GBS patients. In the autopsy series of Asbury *et al.* (1969) this was prominent in all 12 cases studied in the first 6 wks of the disease. However, Brechenmacher *et al.* (1987) found lymphocytes in the endoneurium of only 5 of 57 peripheral nerve biopsies from patients with GBS. Since the nerve biopsy findings might be an artefact of sampling, we report 9 cases of GBS with postmortem examinations and review the 10 single case reports which have been published since the influential paper of Asbury *et al.* (1969). The picture which emerges is that GBS has more than one pathological substrate: lymphocytic infiltration is prominent in some cases, but sparse in others. These conclusions lead to a discussion of possible differences in pathogenesis in relation to the experimental models.

MATERIAL AND METHODS

Patients

We studied available postmortem material from all the patients with GBS who had been encountered during a prospective study of acute idiopathic neuropathy in south-east England in 1983–1984 (Winer *et al.*, 1988) or who had died in Guy's Hospital between 1981 and 1989 and undergone postmortem examination. In addition, postmortem material from Case 6 was made available from another hospital in 1989. One patient presented in our survey of cases of acute neuropathy (Winer *et al.*, 1988) with clinical and neurophysiological evidence of a demyelinating neuropathy and subsequently underwent postmortem examination. This case was excluded because later during his illness he developed bilateral optic atrophy and auditory and visual evoked action potentials became absent. Autopsy revealed extensive CNS as well as peripheral nerve myelin loss and the case was considered to represent an example of encephalomyeloradiculoneuropathy and not GBS. The hospital records of all cases were reviewed. All had been diagnosed as having GBS by a neurologist and fulfilled recognized diagnostic criteria for GBS (Asbury *et al.*, 1978). Appropriate tests had been undertaken to exclude metabolic and toxic causes of neuropathy, including porphyria. Neurophysiological studies were conducted in all cases except Case 5 and suggested a demyelinating process in at least one nerve segment.

Postmortem material was collected between 18 and 24 h after death except in Case 7 when the interval was 3 days. When available, the brain, spinal cord including cauda equina and dorsal root ganglia, and some peripheral nerves were fixed in buffered formol saline. A few samples of peripheral nerve and spinal roots were fixed in 2.5% glutaraldehyde in phosphate buffer for electron microscopy. In 1 patient samples of peripheral nerve were fresh frozen in liquid nitrogen for immunocytochemistry. The study was carried out retrospectively and the material collected could not be standardized. Cranial nerves and spinal roots were dissected and processed separately from the brainstem and spinal cord. For light microscopy, blocks were embedded in paraffin, and sections were stained with haematoxylin and eosin, luxol fast blue and cresyl violet for myelin, haematoxylin and Van Gieson for connective tissue and the silver impregnation technique of Glees and Marsland for axons. Sections of spinal cord were stained for glial fibrillary acid protein. The severity of infiltration was graded 0 = absent, + = mild, ++ = moderate and +++ = severe. The extent of demyelination or axonal degeneration was graded 0 = absent, + = mild (up to 24% of fibres affected), ++ = moderate (25–50% affected) and +++ = severe (more than 50% affected). Axonal degeneration was indicated by swelling, beading, fragmentation or complete loss. For electron microscopy, glutaraldehyde-fixed material was postfixed in osmium tetroxide, processed and embedded in resin. Semithin sections were stained with toluidine blue. Ultrathin sections were stained with uranyl acetate and lead acetate for electron microscopy.

Formalin-fixed paraffin blocks of peripheral nerve were available for immunocytochemistry from 6 of the 9 cases; 1–6 nerves were examined from each case. Control peripheral nerves were taken at autopsy from 5 subjects with no history of neuropathy. Cell counts were made on 6 μm sections stained by the indirect immunoperoxidase method. A mixture of monoclonal antibodies, PD7/26 and 2B11, was used to detect cells expressing the leucocyte common antigen, which is a 200 kDa glycoprotein (CD45) expressed on most leucocytes derived from bone marrow. T cells were labelled with UCHL1, a monoclonal antibody which recognizes an antigen of 180–185 kDa present on a subpopulation of T cells (Smith *et al.*, 1986). It is a reliable marker for normal and neoplastic T cells in paraffin sections (Linder *et al.*, 1987). Sections for staining with PD7/2B11 were preincubated with trypsin for 5 min. The areas of the endoneurium and epineurium were measured using a Hewlett Packard 8613 microcomputer (Hewlett Packard personal computer division, Corvallis, OR, USA) with 'Imagam' basic quantitation software. Input was via a camera lucida and Summagraphics bit pad (Summagraphics Corporation, Fairfield, Connecticut, USA). Frozen sections from Case 4 were examined by the indirect immunoperoxidase or biotin-avidin methods for leucocytes (PD7/2B11), T cells (UCHT1), T cell subsets CD4 (Leu 3a) and CD8+ (UCHT4), B lymphocytes (To15), macrophages (EBM11 DAKO) and HLA-class II (L243, Becton Dickinson) and for deposits of IgG, IgM, IgA. Paraffin sections from the same case were also stained for macrophages (HAM56, Enzobiochem), B cells (L26 DAKO) and HLA-Class II (LN3 Biotest).

CASE REPORTS

Case 1

A 72-yr-old man was admitted to hospital with paraesthesiae and numbness of his extremities for 7 days and progressive weakness of his legs for 3 days. He had had a chest infection 2 wks before the onset of these symptoms. Diabetes mellitus had been treated for 7 yrs with diet and oral hypoglycaemic agents. He had been treated with frusemide for chronic left ventricular failure since a myocardial infarction 5 yrs earlier. Examination showed normal cranial nerves, marked tetraparesis especially affecting the proximal muscles, with depressed upper limb and absent lower limb tendon reflexes. Light touch and vibration sense was impaired distally in upper and lower limbs. He was unable to walk. The cerebrospinal fluid (CSF) contained no cells and its protein content was 0.4 g/l. The sural nerve sensory action potential (SAP) was absent, and radial SAP amplitude 5 μV. Right median nerve forearm maximum motor conduction velocity (MNCV) was 58 $m \cdot s^{-1}$ and distal latency 3.9 ms. The right abductor pollicis brevis muscle action potential (MAP) was desynchronized and its amplitude reduced to 0.28 mV following stimulation at the wrist and 0.20 mV following stimulation at the elbow. A dispersed abductor hallucis MAP, amplitude 0.1 mV, was elicited by stimulating the tibial nerve at the ankle after a latency of 11.2 ms. He was managed with routine supportive treatment. He had a cardiac arrest 2 days after admission. He was resuscitated and ventilated but did not regain consciousness and died the following day, 10 days after the onset of neuropathy.

Postmortem examination showed ischaemic heart disease with congestive heart failure and diabetic nephropathy. At the request of the relatives the brain was not examined. Blocks were taken from the spinal cord, posterior root ganglia, anterior and posterior roots of the cauda equina, left sural, tibial and common peroneal, right sciatic and right median nerves and right brachial plexus. All nerves examined, other than the anterior roots, showed demyelination. The left sural nerve, which was most extensively affected, also showed mild axonal damage affecting some fascicles. There was an increase in cellularity with increased numbers of Schwann cells and inflammatory cells. The inflammatory cells, consisting of lymphocytes and macrophages, were present diffusely within the endoneurium, and around endoneurial blood vessels. There were inflammatory cells infiltrating the wall of a small endoneurial vessel in the brachial plexus, suggestive of vasculitis, but no fibrinoid necrosis was seen and haemosiderin could not be demonstrated around the vessel with a Perl's stain. In the sural and sciatic nerves mild perivascular inflammatory cell cuffing was seen around blood vessels in the epineurium. There was mild bilateral posterior column degeneration with astrocytosis in the spinal cord. The anterior horn cells, dorsal root ganglia and spinal root axons appeared normal in paraffin sections. Toluidine blue stained resin sections of roots and peripheral nerves, however, showed moderate to severe depletion of myelinated fibres, and a few macrophages laden with myelin debris scattered in the endoneurium. There were varying degrees of vesicular dissolution of myelin in all the sections.

Case 2

A 13-yr-old girl was admitted to hospital with paraesthesiae and progressive weakness of her lower limbs for 5 days. Weakness progressed so that by the third day after the onset she was bed bound and on the day of admission she had early respiratory failure. She had been immunized with tetanus toxoid 10 days before the onset. Examination on admission revealed an alert young girl with normal cranial nerves, tetraparesis affecting the lower limbs, in which movements were reduced to a flicker, more than the upper, absent tendon reflexes and impaired vibration sense in all limbs. On the day after admission the MAP evoked in extensor digitorum brevis by stimulation of the deep peroneal nerve at the ankle was dispersed with an amplitude of 0.65 mV compared with 0.25 mV following stimulation at the knee. The right peroneal nerve distal motor latency was delayed (15 ms) and MNCV slowed (30 $m \cdot s^{-1}$). The CSF contained 16 lymphocytes/μl and 0.75 g/l protein. She developed bulbar paralysis and respiratory failure on the day after admission and had to be ventilated. She was treated with 4 plasma exchanges between the second and ninth days after admission. On the ninth day after admission a tracheostomy was performed after which she had a cardiac arrest and did not regain consciousness. A frontal burr hole was performed on the following day and intracranial pressure was monitored continuously. She died 6 days later, 21 days after the onset of neuropathy.

Postmortem examination showed severe pulmonary oedema and bilateral bronchopneumonia. Blocks were taken from the frontal and occipital lobes, cerebellum, midbrain, pons, medulla, cervical, thoracic and lumbar spinal cord, left cranial nerves II, III and IV, one posterior root ganglion and its attached root, sciatic nerve, and skeletal muscle. Sections of brain and spinal cord showed meningitis but no organisms were identified. There was no demyelination in the optic nerve, brain or spinal cord. Spinal anterior horn cells were normal. There was moderate loss of ganglion cells and a mild lymphocyte infiltrate with nodules of Nageotte in the posterior root ganglion. Demyelination was present in cranial nerves III and IV but axons were well preserved. There was extensive demyelination in nerve and posterior spinal nerve roots with much less axon damage, although in all there were some beaded axon fragments. The anterior spinal nerve roots showed much less demyelination and the axons were well preserved. There was an increase in the number of Schwann cell nuclei and small aggregates of lymphocytes and macrophages were seen in the endoneurium and around endoneurial blood vessels of all the peripheral nerve tissue studied other than the anterior spinal nerve roots. Skeletal muscle showed neurogenic atrophy.

Case 3

A 72-yr-old man was admitted to hospital with progressive weakness of his legs for 2 days. He had had a common cold and respiratory infection 2 wks before the onset. He had been treated with methyldopa for hypertension for 3 yrs. Examination showed normal cranial nerves, severe flaccid tetraparesis with only a flicker of movement in his limbs, absent tendon reflexes and distal sensory loss in the limbs. CSF examination showed no cells and 3.8 g/l protein. Distal motor latency was 10.4 ms in the right median nerve, and 10 ms in the right tibial nerve. MNCV was slowed to 26 $m \cdot s^{-1}$ in the median and to 40 $m \cdot s^{-1}$ in the tibial nerve. F waves were absent. The right radial SAP amplitude was 3 μV and the right sural SAP was absent. He developed respiratory paralysis and was ventilated on the sixth day after the onset of the neuropathy. A tracheostomy was performed on the following day. He developed episodes of atrial flutter, hypotension and renal failure treated with peritoneal dialysis. He also developed fulminant bronchopneumonia, urinary tract infection, septicaemia and shock, and died 29 days after the onset of neuropathy.

At postmortem, blocks were taken from the brainstem, spinal cord, cranial nerves III, VII, VIII, X and XII, spinal roots, left median and sural and right tibial nerves. The brain was normal. The vagus nerve showed mild demyelination with well preserved axons but no inflammation. Other cranial nerves were normal. There was loss of anterior horn cells in the spinal cord with chromatolysis of a few surviving cells. Peripheral nerves and spinal nerve roots showed extensive demyelination and moderate axonal loss and mild diffuse endoneurial inflammatory cell infiltration. The cellularity was increased in the affected nerves, mainly due to an increase in the number of Schwann cells. Resin-embedded sections showed multifocal loss of myelinated fibres and occasional macrophages within the endoneurium and sometimes within the basal lamina. Many surviving fibres, especially in spinal roots, exhibited splitting and vesicular dissolution of myelin sheaths.

Case 4

A 74-yr-old man was admitted with paraesthesiae and progressive weakness of his limbs for 1 day. He had had an influenza vaccination 31 days and a chest infection 21 days before admission. He was febrile and mildly dysarthric but alert and conscious. He had a severe areflexic flaccid tetraparesis. Vibration sense was absent up to both knees. The CSF contained 2 lymphocytes/μl and 0.9 g/l protein. Nerve conduction studies revealed prolonged distal motor latencies in the left median (4.6 ms) and tibial (7.5 ms) nerves, and absent MAPs following stimulation of those nerves at the elbow and knee. No MAP could be elicited by stimulation of the left ulnar nerve at the elbow, but the distal motor latency and conduction velocity were normal in the right ulnar nerve. The left radial nerve SAP (7 μV) and sural nerve SAP (2 μV) were small. The tetraparesis and bulbar palsy became worse and he required ventilation on the seventh day of the illness. He developed a fulminant chest infection, and septicaemia and acute renal failure, treated with antibiotics and intermittent peritoneal dialysis. He worsened so that the only residual movements were eye and neck movements. He developed paroxysmal atrial fibrillation and rapid fluctuations of blood pressure. He sustained an asystolic cardiac arrest during the replacement of a nasogastric tube 30 days after the onset of neuropathy and could not be resuscitated.

Postmortem examination showed pulmonary oedema, bilateral pleural effusions and peripheral oedema consistent with renal failure. Samples of median and tibial nerves, brachial plexus, cauda equina roots and a posterior root ganglion were taken. There was severe demyelination with mild axonal degeneration and a moderate diffuse and perivascular endoneurial inflammatory cell infiltrate consisting of lymphocytes and macrophages, in the median and tibial nerves (fig. 1). In the spinal nerve roots and brachial plexus there was mild focal demyelination with well preserved axons and a mild predominantly perivascular endoneurial inflammatory cell infiltrate. There was moderate ganglion cell loss with a sparse lymphocytic infiltrate and nodules of Nageotte in the posterior root ganglion. Resin sections of median and posterior tibial nerves, brachial plexus and spinal nerve roots showed variable degrees of myelinated fibre loss and sparse macrophage infiltration. There were occasional demyelinated axons. Myelin sheaths were often split or undergoing vesicular dissolution.

Case 5

A 63-yr-old priest developed an upper respiratory tract infection lasting 1 wk. One week later he was admitted to hospital with paraesthesiae of his fingers and weakness for 1 day. Examination revealed moderate

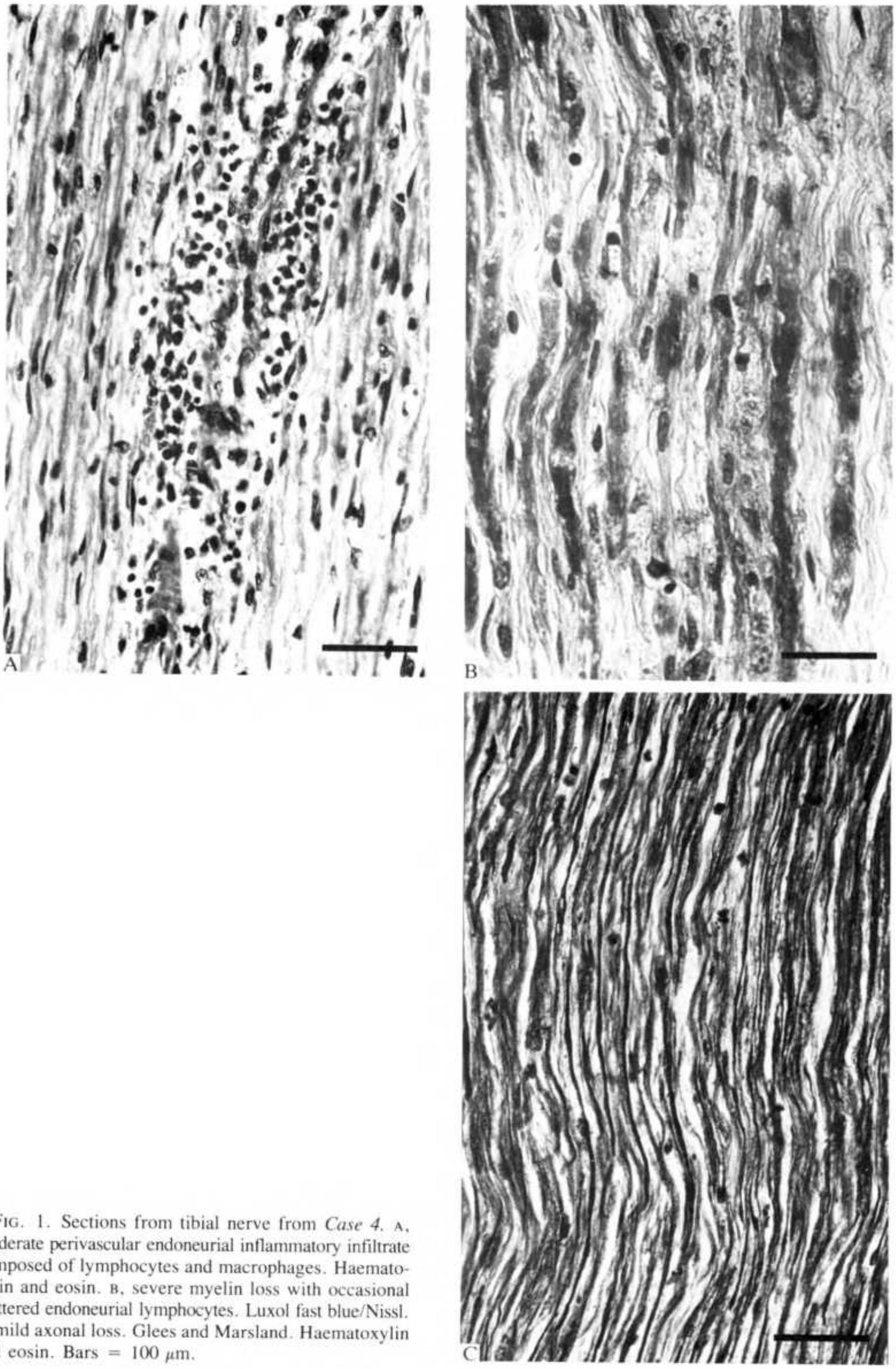

FIG. 1. Sections from tibial nerve from *Case 4*. A, moderate perivascular endoneurial inflammatory infiltrate composed of lymphocytes and macrophages. Haematoxylin and eosin. B, severe myelin loss with occasional scattered endoneurial lymphocytes. Luxol fast blue/Nissl. C, mild axonal loss. Glees and Marsland. Haematoxylin and eosin. Bars = 100 μm.

proximal weakness of all extremities, absent ankle jerks and unsteady gait. By the next day he had developed bilateral ptosis, bilateral facial palsy, weak jaw closure, bulbar palsy, and severe areflexic tetraparesis. The CSF contained 1 lymphocyte per μl and 0.1 g/l protein. He developed wide fluctuations in blood pressure and later that day had to be ventilated. His subsequent course was complicated by episodes of pneumothorax requiring intercostal drainage, chest and urinary infections treated with antibiotics, and ischaemic electrocardiographic changes. On the 21st day after the onset he was alert and able to communicate by nodding slightly despite being ventilated. He had a marked left ptosis and sluggish pupil responses to light but normal eye movements. There was weak jaw closure, bilateral almost complete facial palsy and an atrophic weak tongue. There was generalized wasting of limb muscles, and flaccid areflexic tetraplegia. He was able to perceive pain and light touch on his extremities. He died 31 days after onset of neuropathy following a further episode of pneumothorax.

Postmortem examination showed bilateral tension pneumothoraces and severe atherosclerosis of the coronary arteries. Blocks were taken from the cerebral hemispheres, cerebellum, brainstem, spinal cord and roots, some cranial nerves (right II, both III and IV, right VIII, both X and XI, and left XII) and right median and left sural nerves. The brain and spinal cord, including cranial nerve nuclei and anterior horn cells were normal. Demyelination of varying severity was seen in all except the optic and auditory nerves Most severely affected were the vagi, right oculomotor, and the median and sural. These nerves also showed some degree of axonal damage and wallerian degeneration. Endoneurial inflammatory cell infiltration was mild and diffuse in most of these nerves (figs 2, 3), although none was seen in the left sural and right vagus nerves. There was a mild increase in the number of Schwann cells.

Case 6

A 44-yr-old man developed paraesthesiae and weakness of his lower and then upper limbs 4 wks after an influenza-type illness On admission 2 wks after the onset he was unable to walk, having a severe flaccid areflexic tetraparesis and distal impairment of pain sensation. He was obese, his vital capacity was reduced and a bladder catheter was inserted. The CSF contained no cells but the protein concentration was 2.2 g/l; electrophoresis showed oligoclonal bands in the gamma globulin region. A tiny dispersed right thenar MAP (30 μV) was elicited by stimulation of the median nerve at the wrist with a markedly prolonged latency (18 ms); the median nerve forearm MNCV was 42 $\text{m} \cdot \text{s}^{-1}$. A small dispersed right hypothenar MAP (250 μV) was recorded with a latency of 8 ms. The right radial nerve SAP was absent. He was treated with 4 plasma exchanges, which removed a total of 9.5 l of plasma and improved. Seventeen days later he had syncopal episode and subcutaneous heparin was started. Eleven days after that he had a cardiac arrest.

Postmortem examination showed thrombosis of the deep leg veins and massive pulmonary embolism. Blocks were taken from the basal ganglia, midbrain, left oculomotor nerve, cervical, thoracic and lumbar spinal cord, posterior root ganglia, anterior and posterior roots and brachial plexus There was mild to moderate demyelination in the anterior and posterior roots of the spinal cord, particularly the lumbar and sacral roots, with well preserved axons. Mild inflammatory cell infiltrates were present in the endoneurium of the affected roots, both diffuse and perivascular (fig. 4) There was mild ganglion cell loss with increase in nodules of Nageotte and mild lymphocytic infiltration in all posterior root ganglia studied (fig. 5). Mild posterior column degeneration with reactive astrocytosis was noted in the spinal cord.

Case 7

A 72-yr-old retired building worker was admitted with muscle pain and progressive weakness of his hands and then legs for 3 days. He had had an influenza-like illness 4 wks earlier. Examination showed mild weakness of trapezius and moderate predominantly proximal weakness of the limbs. Tendon reflexes were absent and sensory examination was normal. He was unable to walk. The CSF on the fourth day of illness contained no cells and 4.5 g/l protein Neurophysiological studies showed evidence of multifocal demyelination and severe denervation; stimulation of the right median nerve at the wrist elicited a MAP amplitude 0.04 mV after 11.5 ms. The ulnar distal motor latency was 7.0 ms and forearm MNCV 37 $\text{m} \cdot \text{s}^{-1}$. The right radial SAP amplitude was 7 μV and its maximum sensory conduction velocity 50 $\text{m} \cdot \text{s}^{-1}$. Profuse fibrillation and positive sharp waves were recorded from right first dorsal interosseous muscle, extensor digitorum communis, gastrocnemius and vastus medialis. Limb movements became reduced to a flicker over the next 3 days, and he also developed bilateral facial and bulbar palsy. He required ventilation on the tenth day and a tracheostomy on the twelfth day after the onset. Repeated chest and urinary tract infections were treated with antibiotics. He gradually improved and was weaned off the ventilator

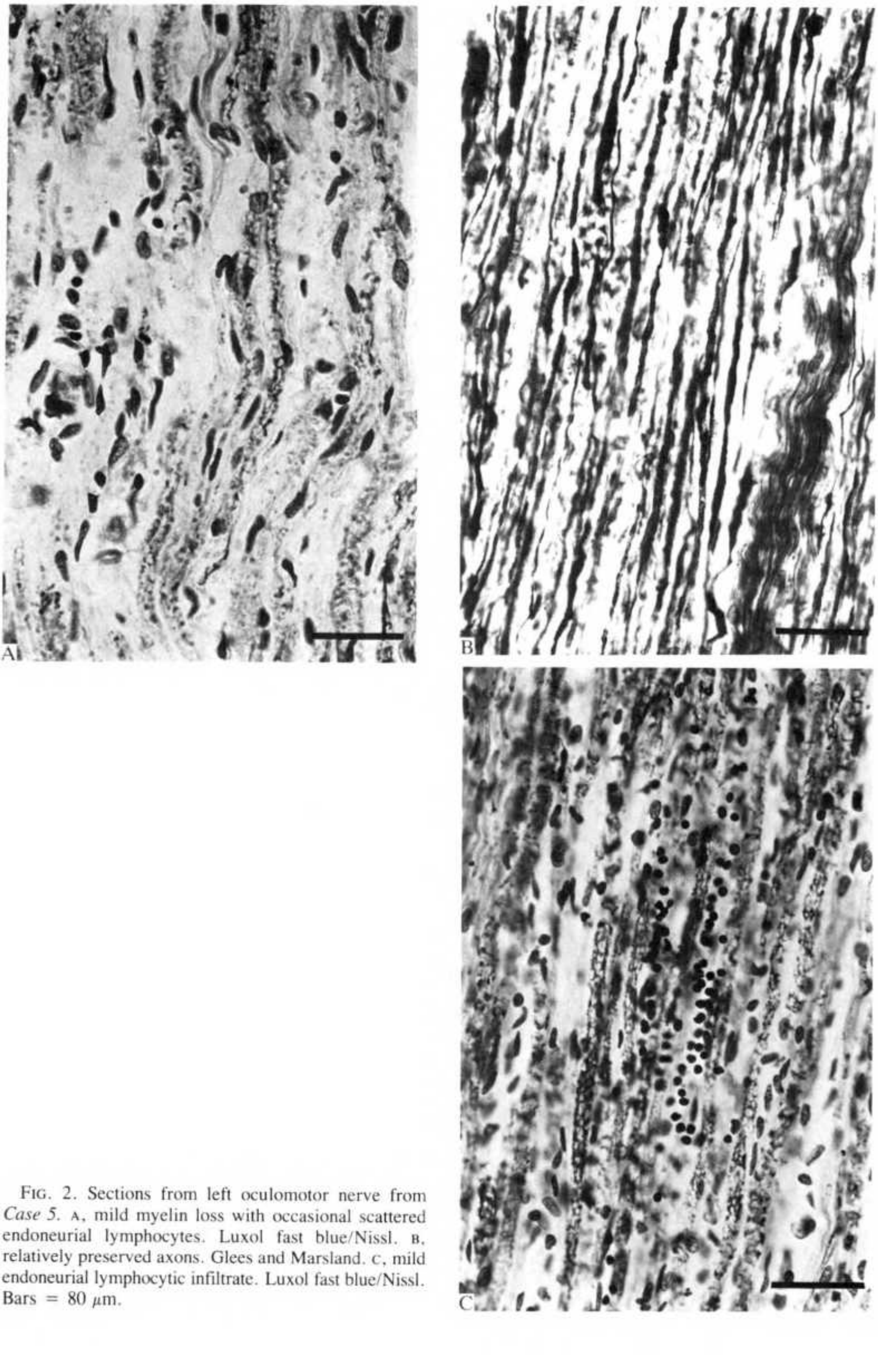

FIG. 2. Sections from left oculomotor nerve from *Case 5.* A, mild myelin loss with occasional scattered endoneurial lymphocytes. Luxol fast blue/Nissl. B, relatively preserved axons. Glees and Marsland. C, mild endoneurial lymphocytic infiltrate. Luxol fast blue/Nissl. Bars = 80 μm.

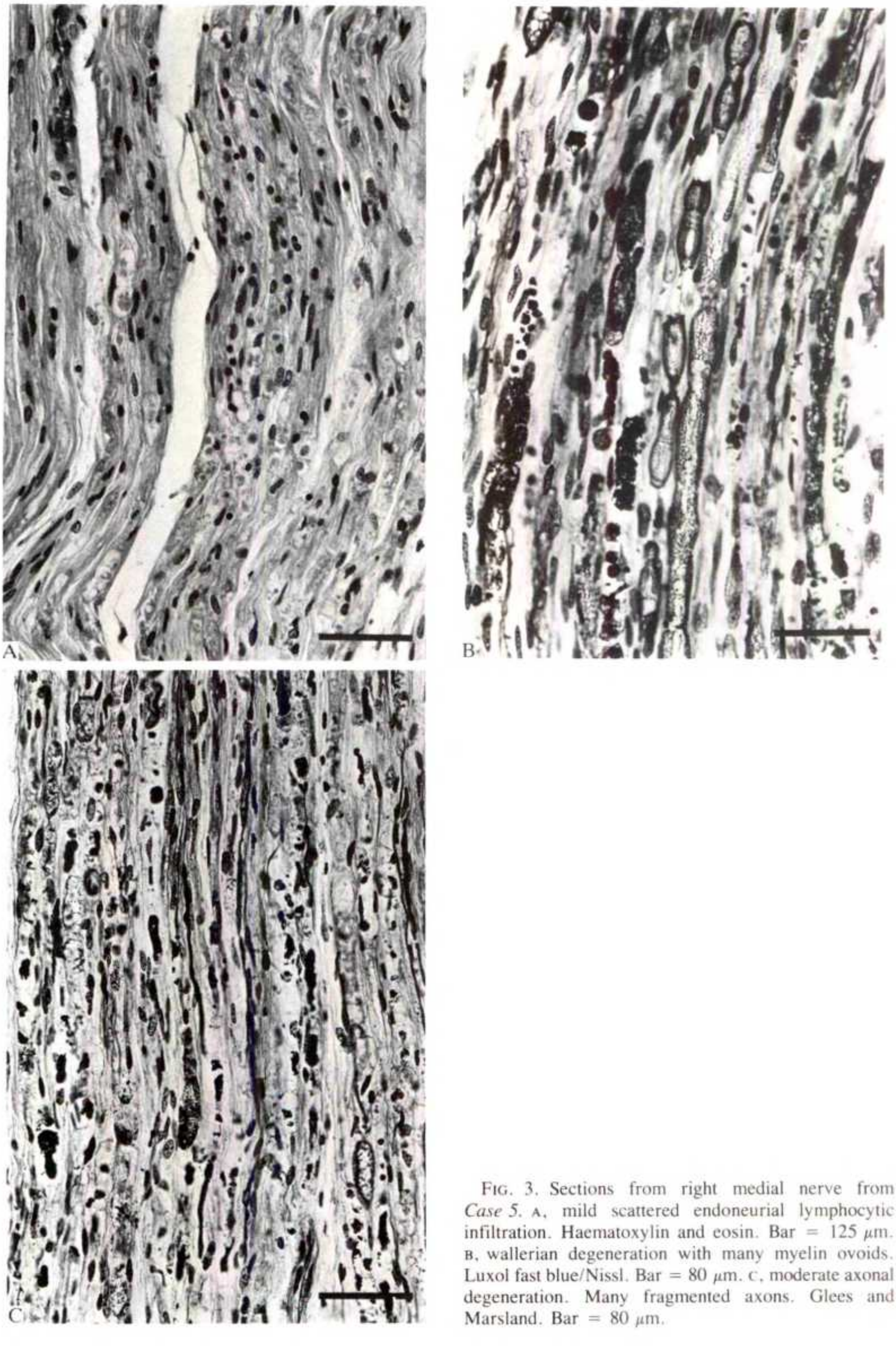

FIG. 3. Sections from right medial nerve from *Case 5*. A, mild scattered endoneurial lymphocytic infiltration. Haematoxylin and eosin. Bar = 125 μm. B, wallerian degeneration with many myelin ovoids. Luxol fast blue/Nissl. Bar = 80 μm. C, moderate axonal degeneration. Many fragmented axons. Glees and Marsland. Bar = 80 μm.

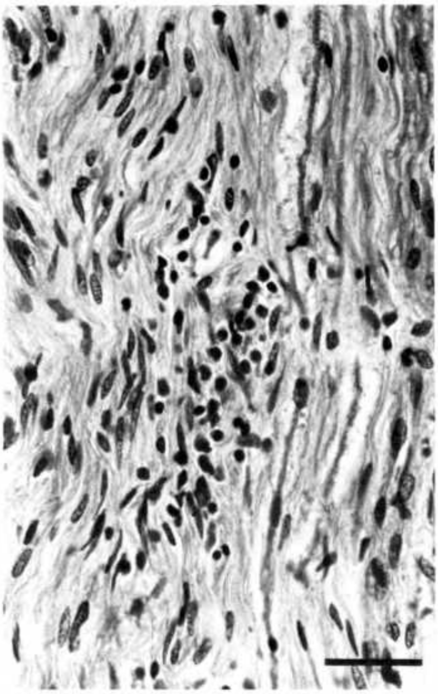

FIG. 4. Posterior spinal nerve root from *Case 6* showing mild endoneurial lymphocytic infiltration. This nerve root displayed moderate myelin loss and no axonal degeneration in other preparations. Haematoxylin and eosin. Bar = 100 μm.

after 11 wks. Intermittent episodes of sinus tachycardia, hypertension and sweating were treated with propranolol. He finally sustained an asystolic cardiac arrest 16 wks after the onset of his neuropathy.

Postmortem examination showed bilateral bronchopneumonia and severe coronary artery atherosclerosis. Sections of vagus, median and sural nerves, lumbar spinal roots, cervical and lumbar sympathetic chain, and skeletal muscle were available. There was mild demyelination in this material but axons were well preserved. Mild inflammatory cell infiltrates composed of lymphocytes and macrophages were present both diffusely in the endoneurium and around blood vessels in the endoneurium and epineurium. Muscles showed neurogenic atrophy.

Case 8

This boy developed chicken pox at age 6 mos, complicated 2 days after the appearance of the rash by otitis media which was treated with erythromycin. Seven days later he became abnormally quiet and floppy, and fed slowly. Examination showed a hypotonic baby who had a weak cry and would not suck. There was a mild convergent squint, weak face and jaw muscles and impaired tongue movements. He was unable to lift his limbs. The tendon reflexes were absent and there was no fasciculation. Plantar responses were absent and there was no response on application of ice to the limbs. Nerve conduction studies showed that MNCV was slowed to 28 $m \cdot s^{-1}$ in the right median nerve but the distal motor latency remained normal. Tibial MNCV was 33 $m \cdot s^{-1}$. The abductor hallucis MAP following stimulation at the ankle was 0.4 mV compared with 0.2 mV following stimulation behind the knee. The median mixed nerve action potential was 20 μV and with a conduction velocity of 41 $m \cdot s^{-1}$. Sampling the right vastus medialis revealed changes of denervation. On the day after admission the CSF contained no cells and 0.2 g/l protein. Two days after admission artificial ventilation was started. Eight days later he began to improve and after another 5 days artificial ventilation was stopped. By 2 mos after admission head control and bulbar function had returned to normal and he went home still having weak limbs. Six mos after the onset the EMG showed slowed MNCV, marked denervation changes and normal SAPs. Limb weakness persisted unchanged despite prednisolone 20 mg daily for 2 mos.

Fourteen mos after the first admission he developed a febrile illness with fever, cough and widespread

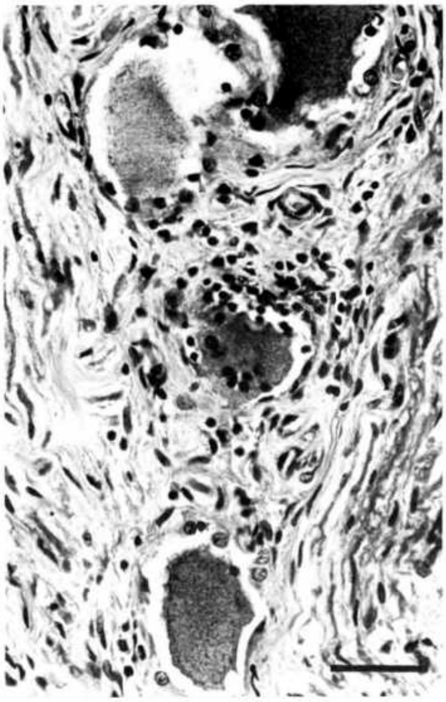

FIG. 5. Posterior root ganglia from *Case 6* showing lymphocytic infiltration. Haematoxylin and eosin. Bar = 100 μm.

rash resembling measles. He was readmitted with an aspiration pneumonia and respiratory failure requiring ventilation. He deteriorated with episodes of bradycardia and hypotension and then loss of response to any stimuli, absent spontaneous eye movements and absent oculocephalic reflexes. One week after the second admission no response could be obtained following stimulation of any peripheral nerve. Sural nerve biopsy revealed almost complete loss of large myelinated nerve fibres and unmyelinated nerve fibres, active wallerian degeneration and many foamy macrophages in the endoneurium. He remained unresponsive. A CT scan showed atrophy but no focal abnormality. Ventilation was discontinued 4 mos after the onset of the second attack and 18 mos after the start of the original illness.

Postmortem examination showed partial collapse of both lungs. Blocks were taken from the cerebral and cerebellar hemispheres, brainstem, thoracic and lumbar spinal cord with posterior root ganglia, anterior and posterior roots, including the cauda equina, both tibial and both axillary nerves and skeletal muscle. There was moderate to severe loss of myelinated axons in all the peripheral nerves examined. The nerve roots showed moderate myelin and axon loss. Mild diffuse endoneurial inflammatory cell infiltration, consisting of lymphocytes and macrophages, was seen in the peripheral nerves and some posterior roots with very occasional perivascular cuffing. The infiltration in the left brachial plexus and one thoracic posterior root was moderately heavy. Inflammation was not seen in any of the anterior roots. Sections of the spinal cord showed marked anterior horn cell loss and bilateral posterior column degeneration with astrocytosis. Neuronal loss was prominent in the posterior root ganglia with mild focal lymphocytic infiltration. The skeletal muscles showed neurogenic atrophy.

Case 9

A 60-yr-old woman was admitted with progressive weakness of her limbs for 2 days and dysphonia, dysphagia and retention of urine for 1 day. She had recovered fully from a diarrhoeal illness 1 wk before admission. Examination revealed bilateral ptosis, bilateral facial palsy, bilateral palatal palsy, severe tetraparesis, absent tendon jerks and normal sensation. She was unable to walk. The CSF on the fourth day of the illness contained no cells and 0.38 g/l protein. Nerve conduction studies on the seventh day showed that no motor response could be elicited by stimulating the right median nerve at the wrist or the tibial nerve at the ankle. MNCV was 30 $m \cdot s^{-1}$ in the right ulnar nerve and distal motor latency 6.2 ms. Right common peroneal MNCV was 45 $m \cdot s^{-1}$ and distal motor latency 8.5 ms. Radial SAP amplitude was 16 μV and sural 8 μV. Her weakness and respiratory paralysis progressed and she had to be ventilated 2 days after admission. She had repeated chest and urinary tract infections and required ventilation for 10 mos. Her cranial nerve palsies gradually recovered and she regained shoulder movement but suddenly developed asystole 1 yr after the onset of the neuropathy.

Postmortem examination showed pulmonary oedema with bronchopneumonia. Blocks were taken from cervical, thoracic and lumbar spinal cord, posterior root ganglia and anterior and posterior roots from the cauda equina. Peripheral nerves were not examined. In the spinal cord there was severe bilateral degeneration of the posterior columns with reactive astrocytosis. In addition, reactive astrocytes were noted in the posterior horns. Anterior horn cells were normal. Mild pallor of the anterior columns at all levels corresponding to the ventral spinocerebellar and spinothalamic tracts was not accompanied by gliosis and was thought to be a staining artefact (fig. 6). The extent of myelin and axon loss from the roots and ganglia was difficult to assess because of poor tissue preservation but there was no inflammatory cell infiltration. There was mild ganglion cell loss in the posterior root ganglia.

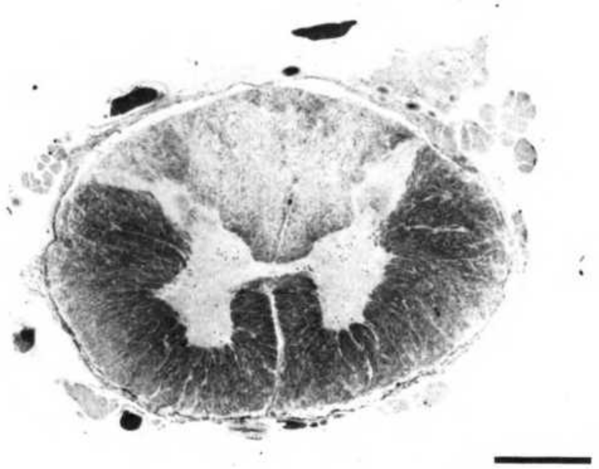

FIG. 6. Section of the lumbar spinal cord from *Case 9* showing bilateral posterior column degeneration. The mild pallor of anterior white columns is a staining artefact. Luxol fast blue/Nissl. Bar = 2.5 mm.

RESULTS

Clinical features

The clinical features of 8 of the 9 cases were typical of GBS. Case 8 differed in being a young child and having 2 attacks. The first attack was typical with the rapid onset of neuropathy with neurophysiological evidence of demyelination and then partial recovery. In the second attack the peripheral nerves became electrically inexcitable and death eventually occurred. Clinical information has been summarized in Table 1. Except in the atypical Case 8, and Case 5 which was not studied neurophysiologically, markedly slowed nerve conduction or conduction block was found in each case. Distally evoked muscle action potentials were small or absent.

TABLE 1 CLINICAL FEATURES OF 9 FATAL CASES OF GBS

Case	*Duration*	*Age (yrs)*	*Sex*	*Steroid treatment*	*Antecedent event*	*Duration to being bed bound (days)*	*Cause of death*	*Notes*
1	10 days	72	M	0	Chest infection	9	Respiratory arrest	Noninsulin-dependent diabetes mellitus
2	21 days	13	F	0 PE	Tetanus toxoid	7	Cardio-respiratory	Intraventricular pressure monitor inserted 7 days before death
3*	29 days	72	M	0	Chest infection	5	Septicaemia	
4*	30 days	74	M	0	Influenza vaccine	2	Asystole	Paroxysmal atrial fibrillation, fluctuating blood pressure
5	31 days	63	M	0	Chest infection	2	Pneumothorax	
6	32 days	44	M	0 PE	Influenza-like illness	14	Pulmonary embolus	
7	4 mos	72	M	0	Influenza-like illness	4	Asystole	Episodes of tachycardia, hypertension and sweating
8	4 mos	1.8	M	+	Chicken pox	–	Cerebral anoxia	2 attacks
9*	1 yr	60	F	0	Gastroenteritis	2	Asystole	

* In series of Winer *et al* (1988). PE = plasma exchange; + = steroid treatment given

Pathological features

Myelin loss in peripheral nerves and spinal nerve roots exceeded axon loss (Table 2) indicating primary demyelination. Occasional examples of demyelinated segments of axons suggesting segmental demyelination were encountered but teased fibre studies were not undertaken. In most cases, axonal degeneration was also evident, and in Case 8 this appeared to have been the primary pathological process. Minor degrees of axonal degeneration and loss were more readily detected in resin than in paraffin sections. Mononuclear inflammatory cell infiltration was seen in peripheral nerves in all except Case 9, but was patchy. The inflammation, which was mild to moderate in severity, was diffuse in some nerves, but focal in others, particularly in a perivascular distribution. In all the cases, many affected nerves showed no signs of inflammation. The inflammatory cells appeared to be lymphocytes and macrophages but their proportions could not be made out with certainty on routine histological preparations. Demyelination was often severe when inflammation was mild or absent.

The most consistent change seen in the CNS was posterior column degeneration in the spinal cord. Anterior horn cell loss was seen in 2 cases and chromatolysis in 1. Loss of nerve cells was noted in posterior root ganglia in 5 cases and was accompanied

TABLE 2. PATHOLOGICAL FEATURES OF 9 FATAL CASES OF GBS

	Mononuclear cell infiltration				*Myelin loss*				*Axonal degeneration*				
Case	*Ant. root*	*Post. root*	*Periph. nerve*	*Cranial nerve*	*Ant. root*	*Post. root*	*Periph. nerve*	*Cranial nerve*	*Ant. root*	*Post. root*	*Periph. nerve*	*Cranial nerve*	*CNS*
1	0	+	+ – + +	NE	0	+	+ – + + +	NE	+	+	+	NE	PCD
2	0	+	+ +	+ – + +	+	+	+ + +	+ +	+	+	0 – + +	0	Meningitis
3	0	0	+	0	0 – +	+ +	+ + +	0 – +	+	+	+ +	0	AHC loss/ chromatolysis
4	+	+	+ – + +	NE	+	+	+ – + + +	NE	+	+	+	NE	NE
5	0	0	+	+	+	+	+ + +	+ – + + +	0	0	+ +	+	Normal
6	+	+	+	0	+ +	+ +	0	0	0	0	0	0	PCD
7	NE	NE	+	0	NE	NE	+	–	NE	NE	0	0	NE
8	0	0 – + +	+ – + +	NE	+ +	+ +	+ + – + + +	NE	+ +	+ +	+ + +	NE	AHC loss PCD
9	0	0	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	PCD

NE = not examined; PCD = posterior column degeneration; AHC = anterior horn cell; 0 = none, + = mild, + + = moderate, + + + = severe.

by inflammatory cell infiltration in 4. Meningitis was a terminal complication in a patient who required intracranial pressure monitoring (Case 2).

Electron microscopy

Although material was obtained for electron microscopy from Cases 1, 3, 4 and 5, the long intervals between death and postmortem examination reduced the usefulness of electron microscopic examination. Vesicular changes affecting the inner, outer or all the layers of the myelin sheath affected many fibres in all the cases (fig. 7A). Such vesicular dissolution of the myelin sheath occurred in the absence of cellular infiltration and could not be distinguished from artefact since similar changes were also common in material obtained from control subjects without neurological disease (fig. 7B). However, sparse endoneurial macrophages laden with myelin debris were present in the GBS (fig. 8) but not the control cases.

Immunohistochemistry

In sections from the nerves of control subjects without neurological disease, very few cells staining with PD7/2B11 (leucocytes) or UCHL1 (T cells) were identified. The number of PD7 positive cells was increased in 5 of the GBS cases (figs 9, 10) and the number of UCHL1 positive cells (figs 11, 12) was increased in 4 cases to more than 3 SDs above the mean count in the normal subjects (Table 3). There were generally similar increases of the same cell types in the endoneurial tissue, but meaningful cell counts were difficult because tissue fragmentation prevented measuring defined areas. Deposits of IgG, IgM and IgA were not identified on the myelin sheaths or elsewhere within the endoneurium.

Peripheral nerve blocks from Case 4 had been kept frozen and were studied with a range of immunocytochemical reagents. Inflammatory cells staining with PD7/2B11

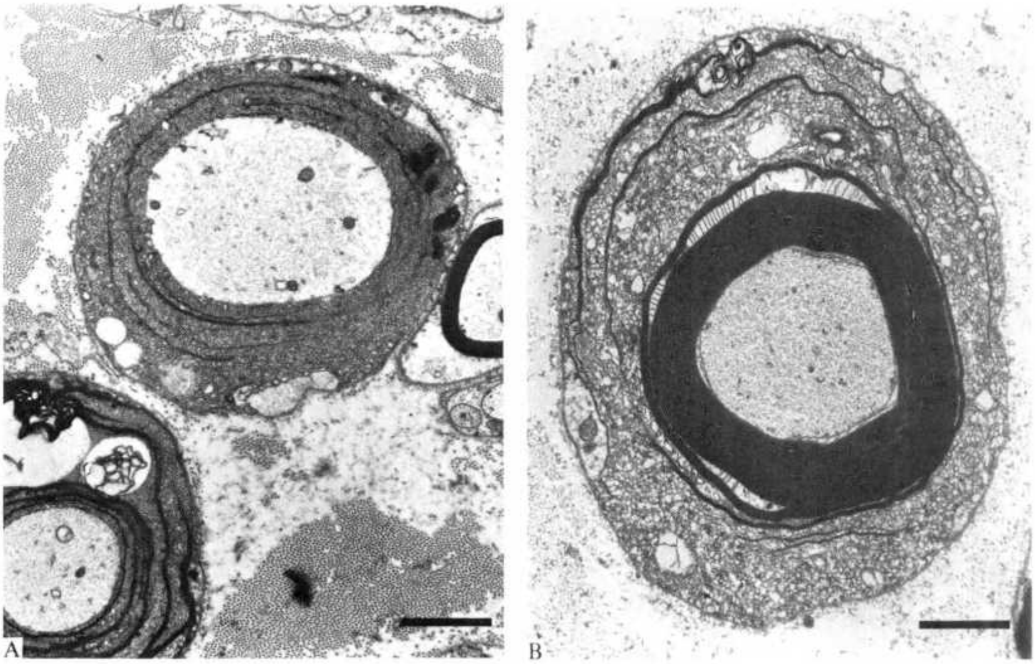

FIG. 7. Electron micrographs of postmortem specimens showing vesicular dissolution of myelin, A, in spinal root of *Case 1* and B, a spinal root from a control subject without known neurological disease. Bars = 2 μm.

were strikingly increased in the endoneurium and the perineurium. In the endoneurium they were often found in the subperineurial space as well as widely scattered. In the epineurium they formed perivascular cuffs around small vessels. Many of these cells were T lymphocytes (UCHT1+). CD4+ (Leu 3a+) as well as CD8 (UCHT4+) subsets were present but CD4+ cells predominated in the epineurial perivascular cuffs in some nerves. The cuffs also contained some B cells (To15+). Large numbers of (EBM11+) macrophages were present in the endoneurium and in the epineurial perivascular cuffs and there were also flattened EBM11+ cells in the perineurium. The macrophages were also HAM56 positive.

DISCUSSION

This is the first series of GBS studied postmortem to be published for 20 yrs and may be the last available in which most cases have not been treated with plasma exchange, immunoglobulin or steroids. The pathological features could be studied with immunohistochemical techniques for the first time and can be interpreted in the light of modern knowledge about experimental antibody and cell-mediated demyelination. The changes were more heterogeneous than had been expected from previous work.

Our cases showed inflammatory cell infiltration in all cases except Case 9, but its extent and degree were less than reported by Asbury *et al.* (1969) who found severe lymphocytic infiltration in all the cases which they studied during the first 6 wks of

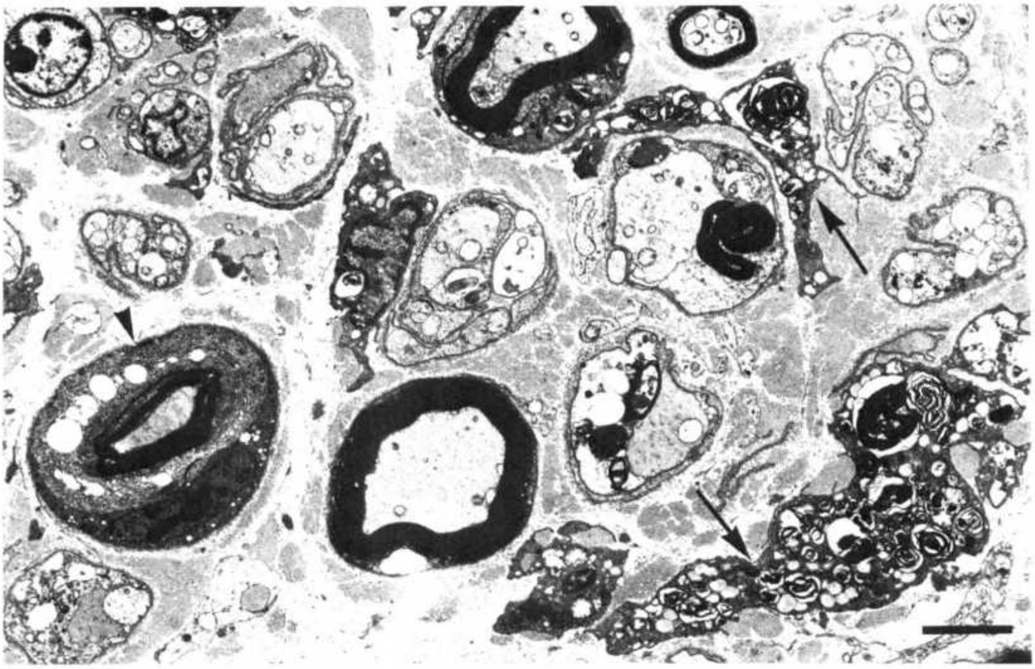

FIG. 8. Electron micrograph of median nerve from *Case 1*, showing 4 demyelinated axons. The myelin sheath of 1 large axon is undergoing vesicular dissolution (arrowhead). Several macrophages, filled with myelin debris, are present in the endoneurium (arrows). Bar = 4 μm.

the illness. The most severe infiltration was found in those cases which they examined within the first 6 days. We did not have the opportunity of examining material from this very early stage. Krücke (1955) had also described intense lymphocytic infiltration of the peripheral nervous system (PNS), especially the spinal roots where they join the dorsal root ganglia, in the early stages of GBS. On the other hand, Haymaker and Kernohan (1949), after studying material from 50 cases ranging from 2 to 46 days after onset, concluded that there was no lymphocytic infiltration until 9 days after the onset, when 'scattered small groups of lymphocytes were occasionally observed'. In a series of 24 cases of neuromuscular paralysis from Mexico, which was probably consistent with GBS, inflammatory lesions were consistently found but were sparse (Ramos-Alvarez *et al.*, 1969). In the individual case reports which have been published since 1969 (*see* Appendix), mononuclear cell infiltration of the PNS has been a constant feature of every case but has usually been mild. In 1 case examined 8 days after onset there was a heavy infiltrate of macrophages with very few lymphocytes (Kanda *et al.*, 1989). Although corticosteroid treatment and possibly plasma exchange might have modified the cellular response in a few of the reported cases (Asbury and Johnson, 1978), the cases reported by Haymaker and Kernohan (1949) would not have been treated with steroids and very few of our cases (Table 1) or the cases reviewed in the Appendix were given either steroids or plasma exchange.

The identity of the inflammatory cell infiltrate in the PNS has not previously been

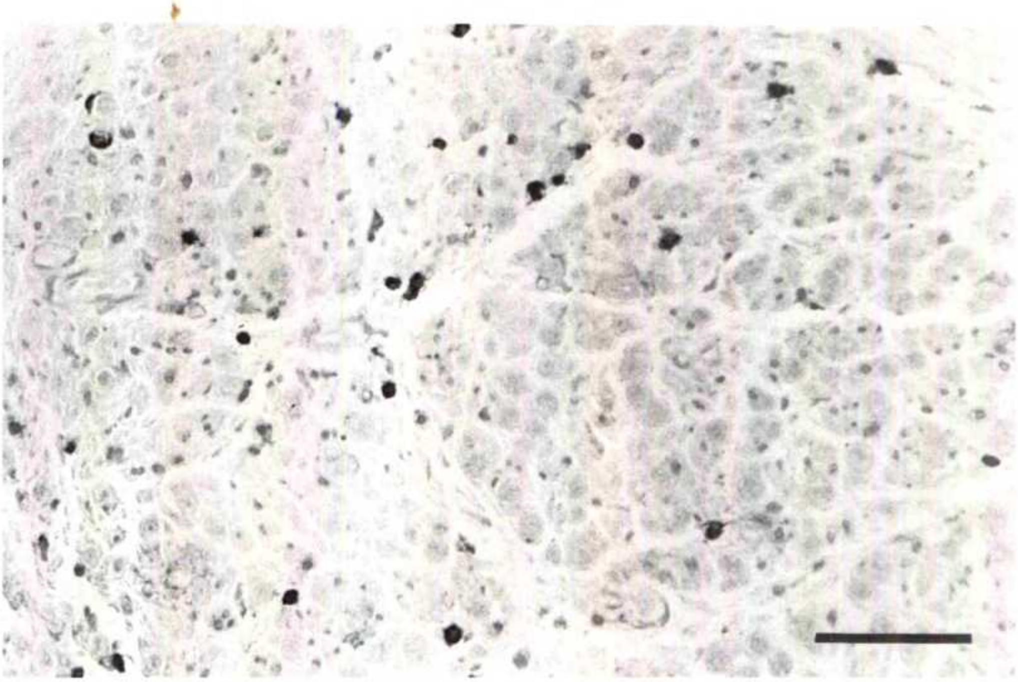

FIG. 9. Leucocytes in the endoneurium. Transverse section from the tibial nerve of *Case 4* immunostained with monoclonal antibodies to leucocyte common antigen (PD7/2B11). Indirect immunoperoxidase method on formalin-fixed paraffin section. Bar = 50 μm.

studied with immunohistochemical techniques in postmortem material. Asbury *et al.* (1969) concluded that many of the larger mononuclear cells in the PNS were lymphoblasts resembling similar cells in the lesions of EAN. In our material, although some of the inflammatory cells had the morphological characteristics of small lymphocytes, it was not possible to assign the larger mononuclear cells confidently to either the lymphocyte or macrophage series. In most of the reports in the Appendix the authors did not make the distinction so that we have had to use the neutral term 'mononuclear cell infiltration'. With a monoclonal antibody directed against the leucocyte common antigen we have shown an increased number of leucocytes (including both macrophages and lymphocytes) in the endoneurium of each of the cases studied in the first 31 days after the onset. There was also an increase in the number of T cells in the endoneurium in the first 29 days (Cases 1, 2, 4) but not in 3 cases with longer survival (Cases 5, 8, 9). The apparent anomaly that more cells stained with the T cell marker than with the leucocyte marker is probably due to the fact that the monoclonal antibody used, PD7, has a reduced sensitivity for detecting leucocytes in paraffin-embedded sections, whereas the antigen recognized by the T cell antibody, UCHL1, is relatively robust. In the frozen material available (Case 4) the infiltrating T cells consisted of both CD4+ and CD8+ subsets and there were a few B cells. Unfortunately, available subset markers do not work well on paraffin sections. Many of the inflammatory cells expressed HLA class II antigens, which were also present in many endoneurial cells, and were increased on the vascular endothelium.

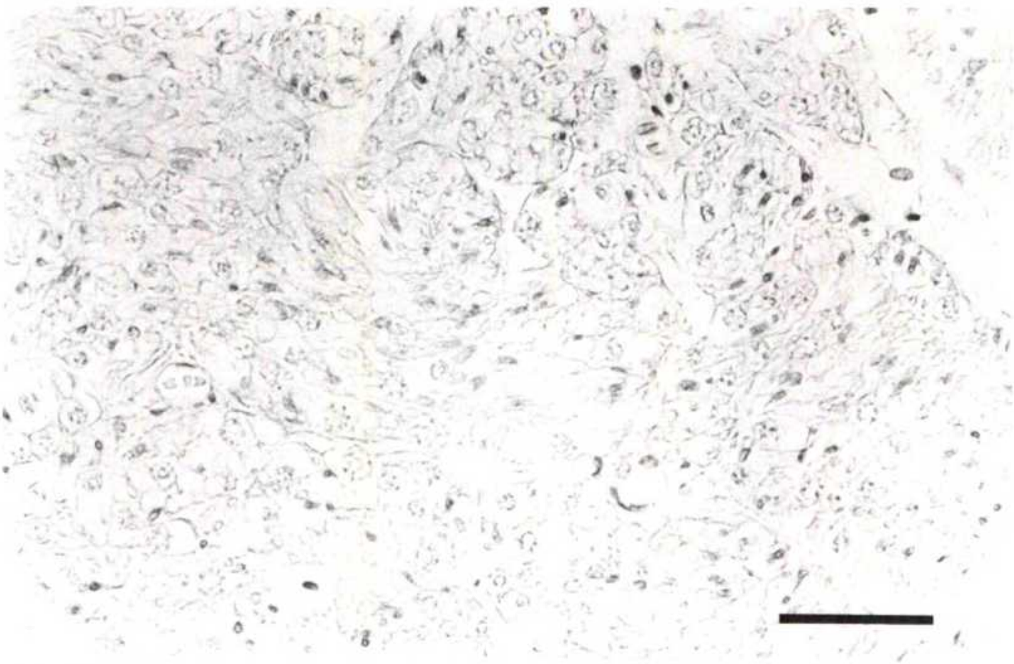

FIG. 10. Transverse section from a nerve from a control subject immunostained as in fig. 9. Bar = 50 μm.

Nerve biopsies from patients with GBS have usually been reported as showing macrophage-associated demyelination with little or no lymphocytic infiltration (Prineas, 1972, 1981; Brechenmacher *et al.*, 1987). In our own series of 10 sural nerve biopsies from patients with GBS, lymphocytic infiltration was discovered in only 3 (R. A. C. Hughes, P. F. Atkinson, S. M. Hall and S. Leibowitz, unpublished). Lymphocytic infiltration was confirmed by immunohistochemical techniques in the sural nerve biopsies in 2 cases of GBS, of which 1 had antibodies to human immunodeficiency virus type I (Cornblath *et al.*, 1990). Since the clinical and pathological evidence suggests that the brunt of the pathology in most cases of GBS falls on the roots, the absence of inflammatory changes from a small sample of a distal peripheral nerve must be interpreted with caution. The sural nerve action potential was abnormal in 33% of 86 neurophysiological studies whereas the median nerve action potential was abnormal in 65%, suggesting that the sural nerve is less often or less severely affected than upper limb sensory nerves (Albers *et al.*, 1985).

Although demyelination has been regarded as the pathological hallmark of GBS, Feasby *et al.* (1986) have reported a case in which the peripheral nerves were inexcitable and postmortem examination confirmed that the major pathological change was axonal degeneration. The second attack which led to the death of our Case 8 resembled that reported by Feasby *et al.* (1986) in that the nerves were electrically inexcitable and the pathological appearances of a sural nerve biopsy and the postmortem examination were those of axonal degeneration. The pathogenesis of this axonal neuropathy presenting as Guillain-Barré syndrome is likely to be different from the more common cases in

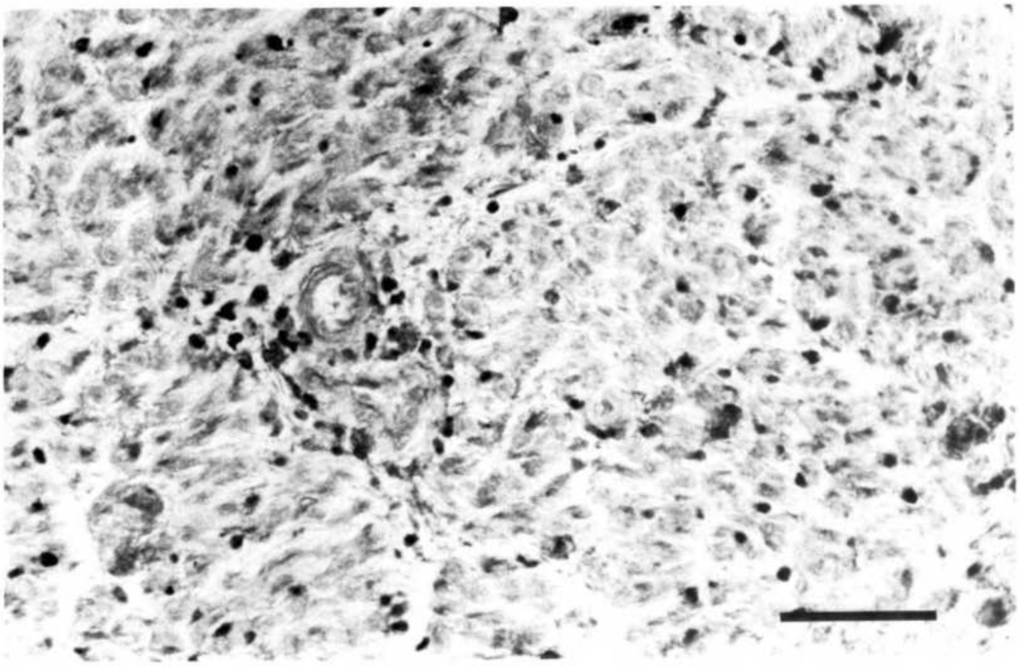

FIG. 11. T lymphocytes in the endoneurium. Transverse section from the brachial plexus of *Case 4* immunostained with monoclonal antibody UCHL1. Bar = 50 μm.

which demyelination is predominant. However, some axonal degeneration is commonly found in biopsies and postmortem examinations of cases of GBS, but in association with inflammation and demyelination. It is likely that this axonal damage occurs as a secondary consequence of particularly severe inflammation, as a so-called 'bystander effect' (Asbury *et al.*, 1969).

It is difficult to overcome the problems of fixation associated with postmortem examination in order to define the ultrastructure of the demyelinating process. In early reports vesicular dissolution in the absence of cellular invasion was thought to be a significant mechanism of myelin breakdown (Wiśniewski *et al.*, 1969; Mei Liu, 1970; Carpenter, 1972). We did not have the opportunity of fixing material until 24 h after death by which time vesicular change was common. Vesicular change was also common in the myelin of patients without neuropathy examined postmortem. Therefore we propose that vesicular disruption of myelin in autopsy material may merely represent postmortem artefact. In studies of nerve biopsies, the major mechanism of myelin breakdown has been a process of macrophage invasion of the Schwann cell basal lamina followed by stripping and phagocytosis of myelin lamellae (Prineas, 1972, 1981). In our ongoing study of 10 biopsies from patients with GBS and in a study of 65 biopsies reported by Brechenmacher *et al.* (1987), extracellular myelin vesicular dissolution has been uncommon.

In keeping with the absence of clinical signs of CNS involvement in our series, no relevant abnormalities were found in the brain. The pathological findings in the spinal

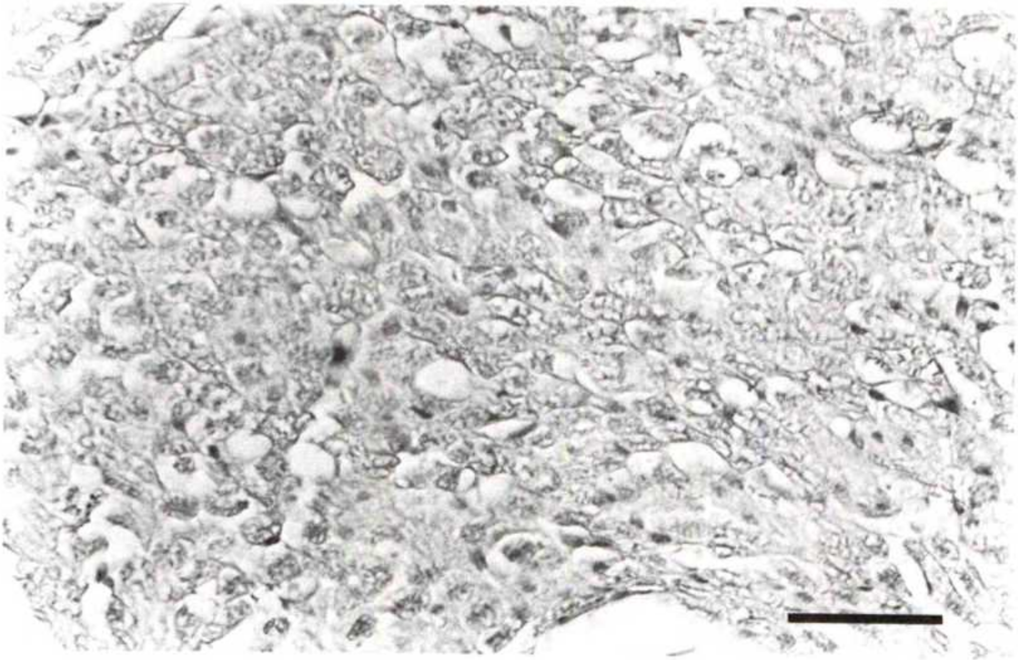

FIG. 12. Transverse section from a nerve from a control subject immunostained as in fig. 11. Bar = 50 μm.

cord could be accounted for by inflammatory lesions affecting the posterior root ganglia and lower motor neurons. In 4 of the 7 cases in which we were able to examine the spinal cord there was posterior column degeneration, consistent with damage to the posterior root ganglion cells. In only 2 cases was there loss of anterior horn cells, of which 1 was the atypical case with severe axonal degeneration. These findings are consistent with earlier reports (Haymaker and Kernohan, 1949; Asbury *et al.*, 1969). They support the idea that the pathology of GBS, although heterogeneous, is confined to the PNS. Cases of GBS associated with CNS lesions, sometimes resembling multiple sclerosis (Lassmann *et al.*, 1981; Best, 1985) are exceptional.

The causes of death in a potentially reversible condition deserve careful consideration. The causes were similar to those reported in clinical series (Winer *et al.*, 1988) and previous postmortem series (Haymaker and Kernohan, 1949; Asbury *et al.*, 1969) and single case reports (*see* Appendix). Three patients died from asystolic cardiac arrest. Two of these deaths occurred despite intensive care and had been preceded by fluctuating blood pressure and other autonomic disturbances which have been recognized as factors predicting a fatal cardiac arrhythmia (Lichtenfeld, 1971; Winer and Hughes, 1988). One of these was a late event in a patient who had remained very disabled. Three patients died from ventilatory complications despite the best available intensive care, 1 from a cardiorespiratory arrest, 1 from a recurrent tension pneumothorax, and 1 from the effects of cerebral anoxia. Another patient died from septicaemia following a chest infection. All these patients had had an acute onset of paralysis so that they were bed bound within a week and required ventilatory support, both factors which predict an

TABLE 3 LEUCOCYTES (PD7/2B11+) AND T CELLS (UCHL1+) IN THE ENDONEURIUM

Controls	*Leucocytes*	*T cells*
1	8.6	
2	0.0	
3	10.0	3.0
4	7.7	2.0
5	2.5	6.0
6	9.5	0.0
Mean (SD)	6.38 (4.12)	2.75 (2.50)
GBS		
1	22^{+}	41^{+}
2	56^{+}	173^{+}
3		
4*	96^{+}	543^{+}
5	20^{+}	4.7
6		
7		
8	5	3.3
9	7	7.7

* In this case there were 82/mm^2 leucocytes and 57/mm^2 T cells in sections from a posterior root ganglion $^{+}$ Increased more than control mean+3 SD.

adverse outcome (Winer *et al.*, 1988). One patient was considered to be in such poor general condition that ventilatory support care was inappropriate and he died of untreated respiratory failure (Case 1). One patient, who had not initially been treated with prophylactic heparin, died from pulmonary embolism at a time when he was recovering. The distally evoked muscle action potentials were small in all 8 cases in which they were recorded, in keeping with the reported adverse prognosis of this neurophysiological measure (Cornblath *et al.*, 1988). None of the patients had any clinical signs of CNS involvement, except for a lowered level of consciousness following incomplete recovery from cardiac arrest in 3 cases (Cases, 1, 2, 8).

The most interesting question raised by our postmortem study is what differences in pathogenesis underlie the differences in pathology. When lymphocytic infiltration is prominent, T cells may be the prime movers as proposed by Asbury *et al.* (1969). Such lymphocytic infiltration closely resembles the histology of EAN which is predominantly due to T cell mediated immunity to myelin P_2 protein (Kadlubowski *et al.*, 1980; Linington *et al.*, 1984; Brosnan *et al.*, 1987). When macrophage-associated demyelination occurs despite a paucity of lymphocytes, it is reasonable to propose that an antibody-mediated mechanism is involved, which might be operating directly by complement fixation and generation of the membrane attack complex. In support of this idea complement-fixing antibodies to myelin have been reported as present in a high proportion of sera from patients with GBS by some authors (Melnick, 1963; Koski *et al.*, 1985). According to Koski *et al.* (1986) nearly all sera contain such antibodies early in the course of GBS. Although a demyelinating neuropathy can be induced in rabbits by immunization with galactocerebroside, and antibodies to galactocerebroside induce demyelination (Saida *et al.*, 1981), complement-fixing antibodies to this antigen are not found in GBS. The antimyelin antibodies identified by Koski react with a neutral glycolipid related to Forssman antigen (Koski *et al.*, 1989). Since T cell and B cell responses usually act in concert, it is likely that in GBS the differing pathogenesis depends on the relative contribution of each.

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REFERENCES

Albers JW, Donofrio PD, McGonagle TK (1985) Sequential electrodiagnostic abnormalities in acute inflammatory demyelinating polyradiculoneuropathy. *Muscle and Nerve*, **8**, 528–539.

Arstila AU, Riekkinen PJ, Rinne UK, Pelliniemi TT, Nevalainen T (1971) Guillain-Barré syndrome: neurochemical and ultrastructural study *European Neurology*, **5**, 257–269.

Asbury AK, Arnason BG, Adams RD (1969) The inflammatory lesion in idiopathic polyneuritis: its role in pathogenesis. *Medicine, Baltimore*, **48**, 173–215.

Asbury AK, Arnason BGW, Karp HR, McFarlin DE (1978) Criteria for diagnosis of Guillain-Barré syndrome. *Annals of Neurology*, **3**, 565–566.

Asbury AK, Johnson PC (1978) Acute idiopathic polyneuritis and related disorders. In· *Pathology of Peripheral Nerve*. Edited by A. K. Asbury and P. C. Johnson. Philadelphia and London: W. B. Saunders, pp. 120–135.

Behar R, Penny R, Powell HC (1986) Guillain-Barré syndrome associated with Hashimoto's thyroiditis. *Journal of Neurology*, **233**, 233–236.

Best PV (1985) Acute polyradiculoneuritis associated with demyelinated plaques in the central nervous system: report of a case. *Acta Neuropathologica, Berlin*, **67**, 230–234.

Brechenmacher C, Vital C, Deminiere C, Laurentjoye L, Castaing Y, Gbikpi-Benissan G *et al.* (1987) Guillain-Barré syndrome: an ultrastructural study of peripheral nerve in 65 patients. *Clinical Neuropathology*, **6**, 19–24.

Brosnan JV, Craggs RI, King RHM, Thomas PK (1987) Reduced susceptibility of T cell-deficient rats to induction of experimental allergic neuritis. *Journal of Neuroimmunology*, **14**, 267–282.

Carpenter S (1972) An ultrastructural study of an acute fatal case of Guillain-Barré syndrome. *Journal of the Neurological Sciences*, **15**, 125–140.

Cornblath DR, Mellits ED, Griffin JW, McKhann GM, Albers JW, Miller RG *et al.* (1988) Motor conduction studies in Guillain-Barré syndrome: description and prognostic value. *Annals of Neurology*, **23**, 354–359.

Cornblath DR, Griffin DE, Welch D, Griffin JW, McArthur JC (1990) Quantitative analysis of endoneurial T-cells in human sural nerve biopsies. *Journal of Neuroimmunology*, **26**, 113–118.

Dehaene I, Martin JJ, Geens K, Cras P (1986) Guillain-Barré syndrome with ophthalmoplegia: clinicopathologic study of the central and peripheral nervous systems, including the oculomotor nerves. *Neurology, Cleveland*, **36**, 851–854.

Feasby TE, Gilbert JJ, Brown WF, Bolton CF, Hahn AF, Kopman WF *et al.* (1986) An acute axonal form of Guillain-Barré polyneuropathy. *Brain*, **109**, 1115–1126.

Haymaker W, Kernohan JW (1949) The Landry-Guillain-Barré syndrome: a clinicopathologic report of fifty fatal cases and a critique of the literature. *Medicine, Baltimore*, **28**, 59–141.

Hughes RAC, Powell HC (1984) Experimental allergic neuritis: demyelination induced by P_2 alone and non-specific enhancement by cerebroside. *Journal of Neuropathology and Experimental Neurology*, **43**, 154–161.

Kadlubowski M, Hughes RAC, Gregson NA (1980) Experimental allergic neuritis in the Lewis rat: characterization of the activity of peripheral myelin and its major basic protein, P_2. *Brain Research, Amsterdam*, **184**, 439–454.

Kanda T, Hayashi T, Tanabe H, Tsubaki T, Oda M (1989) A fulminant case of Guillain-Barré syndrome: topographic and fibre size related analysis of demyelinating changes. *Journal of Neurology, Neurosurgery and Psychiatry*, **52**, 857–864.

Koski CL, Humphrey R, Shin ML (1985) Anti-peripheral myelin antibody in patients with demyelinating neuropathy: quantitative and kinetic determination of serum antibody by complement component 1 fixation. *Proceedings of the National Academy of Sciences of the USA*, **82**, 905–909.

Koski CL, Gratz E, Sutherland J, Mayer RF (1986) Clinical correlation with anti-peripheral-nerve myelin antibodies in Guillain-Barré syndrome *Annals of Neurology*, **19**, 573–577.

Koski CL, Chou DKH, Jungalwala FB (1989) Anti-peripheral nerve myelin antibodies in Guillain-Barré syndrome bind a neutral glycolipid of peripheral myelin and cross-react with Forssman antigen. *Journal of Clinical Investigation*, **84**, 280–287.

Krucke W (1955) Die primär-entzündliche Polyneuritis unbekannter Ursache. In: *Handbuch der Speziellen Pathologischen Anatomie und Histologie*, Volume 13, Part 5 *Erkrankungen des Peripheren Nervensystems*. Edited by O. Lubarsch, F. Henke and G. Rössle. Berlin: Springer, pp 164–182.

Lampert PW (1969) Mechanism of demyelination in experimental allergic neuritis: electron microscopic studies. *Laboratory Investigation*, **20**, 127–138.

Landry O (1859) Note sur la paralysie ascendante aigue. *Gazette Hebdomadaire de Médécine et de Chirurgie*, **6**, 472–488.

Lassmann H, Budka H, Schnaberth G (1981) Inflammatory demyelinating polyradiculitis in a patient with multiple sclerosis. *Archives of Neurology, Chicago*, **38**, 99–102.

Lichtenfeld P (1971) Autonomic dysfunction in the Guillain-Barré syndrome. *American Journal of Medicine*, **50**, 772–780

Linder J, Ye Y, Harrington DS, Armitage JO, Weisenburger DD (1987) Monoclonal antibodies marking T lymphocytes in paraffin-embedded tissue. *American Journal of Pathology*, **127**, 1–8.

Linington C, Izumo S, Suzuki M, Uyemura K, Meyermann R, Wekerle H (1984) A permanent rat T cell line that mediates experimental allergic neuritis in the Lewis rat *in vivo*. *Journal of Immunology*, **133**, 1946–1950.

Mei Liu H (1970) Ultrastructure of remyelination of peripheral nerves in Landry-Guillain-Barré syndrome. *Acta Neuropathologica, Berlin*, **16**, 262–265.

Melnick SC (1963) Thirty-eight cases of the Guillain-Barré syndrome. an immunological study. *British Medical Journal*, **i**, 368–373.

Phillips MS, Stewart S, Anderson JR (1984) Neuropathological findings in Miller Fisher syndrome. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 492–495.

Powell HC, Braheny SL, Hughes RAC, Lampert PW (1984) Antigen-specific demyelination and significance of the bystander effect in peripheral nerves. *American Journal of Pathology*, **114**, 443–453

Prineas JW (1972) Acute idiopathic polyneuritis: an electron microscope study. *Laboratory Investigation*, **26**, 133–147.

Prineas JW (1981) Pathology of the Guillain-Barré syndrome. *Annals of Neurology*, **9**, Supplement, 6–19.

Ramos-Alvarez M, Bessudo L, Sabin AB (1969) Paralytic syndromes associated with noninflammatory cytoplasmic or nuclear neuronopathy: acute paralytic disease in Mexican children, neuropathologically distinguishable from Landry-Guillain-Barré syndrome. *Journal of the American Medical Association*, **207**, 1481–1492.

Rostami A, Brown MJ, Lisak RP, Sumner AJ, Zweiman B, Pleasure DE (1984) The role of myelin P_2 protein in the production of experimental allergic neuritis. *Annals of Neurology*, **16**, 680–685.

Saida T, Saida K, Dorfman SH, Silberberg DH, Sumner AJ, Manning MC *et al.* (1979) Experimental allergic neuritis induced by sensitization with galactocerebroside. *Science*, **204**, 1103–1106

Saida T, Saida K, Silberberg DH, Brown MJ (1981) Experimental allergic neuritis induced by galactocerebroside. *Annals of Neurology*, **9**, Supplement, 87–101

Smith SH, Brown MH, Rowe D, Callard RE, Beverley PCL (1986) Functional subsets of human helper-inducer cells defined by a new monoclonal antibody, UCHL1. *Immunology*, **58**, 63–70.

Stoll G, Schwendemann G, Heininger K, Köhne W, Hartung H-P, Seitz R *et al.* (1986) Relation of clinical, serological, morphological, and electrophysiological findings in galactocerebroside-induced experimental allergic neuritis. *Journal of Neurology, Neurosurgery and Psychiatry*, **49**, 258–264.

Van Zandycke M, Martin J-J, Gaer LV, Van den Heyning P (1982) Facial myokymia in the Guillain-Barré syndrome: a clinicopathologic study. *Neurology, New York*, **32**, 744–748.

WAKSMAN BH, ADAMS RD (1955) Allergic neuritis: an experimental disease of rabbits induced by the injection of peripheral nervous tissue and adjuvants. *Journal of Experimental Medicine*, **102**, 213–236.

WAKSMAN BH, ADAMS RD (1956) A comparative study of experimental allergic neuritis in the rabbit, guinea pig, and mouse. *Journal of Neuropathology and Experimental Neurology*, **15**, 293–333.

WINER JB, HUGHES RAC (1988) Identification of patients at risk of arrhythmia in the Guillain-Barré syndrome. *Quarterly Journal of Medicine*, **68**, 735–739.

WINER JB, HUGHES RAC, OSMOND C (1988) A prospective study of acute idiopathic neuropathy. I. Clinical features and their prognostic value. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 605–612.

WIŚNIEWSKI H, TERRY RD, WHITAKER JN, COOK SD, DOWLING PC (1969) Landry-Guillain-Barré syndrome: a primary demyelinating disease. *Archives of Neurology, Chicago*, **21**, 269–276.

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APPENDIX

*Postmortem studies of Guillain-Barré syndrome published since 1969**

Reference	*Duration (days)*	*Age (yrs)*	*Sex*	*Steroid treatment*	*Cause of death*	*Mononuclear cell infiltration*		
						Anterior roots	*Posterior roots*	*Peripheral nerve*
Kanda *et al* (1989)	8	47	M	PE	Sudden bradycardia	+++	+++	+++
Arstila *et al* (1971)	11	66	M	ACTH	Pulmonary embolism	+	+	
Wiśniewski *et al* (1969)	14	21	F	0	Cardiac arrest	+	+	+
Van Zandycke *et al* (1982)	17	55	F	0	Sudden	+	++	
Mei Liu (1970)	17	21	F	0	Tracheostomy haemorrhage			
Carpenter (1972)	18	47	M	+	Pneumonia	++	+	+
Ponsby *et al* (1986)	28	64	F	0	Septicaemia	+	+	+
Phillips *et al* (1984)	30	67	F	0	Sudden	+	+	+
Dehaene *et al* (1986)	40	52	F	0	Septicaemic shock		+	+
Prineas (1972)	50			+	Cardiac arrest	0	0	
Bohar *et al* (1986)	54	73	M	+	Sudden	++	++	0
Best (1985)	63	72	F	0	General deterioration	++	++	

Reference	*Demyelination*		*Axonal degeneration*				*CNS*	*Notes*
	Anterior roots	*Posterior roots*	*Cranial nerves*	*Anterior roots*	*Posterior roots*	*Peripheral nerves*		
Kanda *et al* (1989)	++	++	++	0	0	0	Brainstem motor nuclei chromatolysis	Small lymphocytes, few
Arstila *et al* (1971)	+	+					Normal	
Wiśniewski *et al* (1969)	+	+	+	0	0	0	Normal	
Van Zandycke *et al* (1982)			+ Facial			+ Facial	Lymphocytic infiltration of spinal cord	Limited EM study only
Mei Liu (1970)								
Carpenter (1972)	+	+	+	0	0	0	Normal	

Reference	*Demyelination*		*Axonal degeneration*				*CNS*	*Notes*
	Anterior roots	*Posterior roots*	*Cranial nerves*	*Anterior roots*	*Posterior roots*	*Peripheral nerves*		
Feasby *et al.* (1986)				+++	+++	+++	Anterior horn cell chromatolysis	
Phillips *et al.* (1984)	++	++	++	0	0	0	Normal	Miller Fisher syndrome
Dehaene (1986)		++	++		0	0	Rare anterior horn cell and oculomotor chromatolysis	
Prineas (1972)	++	++		+	+			Remyelination prominent
Baher *et al.* (1986)	+	+	0	0	0	0	Normal	
Best (1985)	++	++		0	0			

* Where no information is entered, no report was provided. PE = plasma exchange. Grades: 0 = none, + = mild, ++ = moderate, +++ = severe.

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THE LONGSTANDING MS LESION

A QUANTITATIVE MRI AND ELECTRON MICROSCOPIC STUDY

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SUMMARY

Important questions remain unanswered about the sequence of events leading to progressive and ultimately irreversible tissue damage in MS. This study was designed to investigate the pathological characteristics of, and function of, the blood-brain barrier within longstanding MS lesions using quantitative and Gd-DTPA enhanced MRI techniques. The ultrastructural appearances of postmortem lesions from a single, separate case of MS have been correlated with the MRI findings. Both MRI and ultrastructural analysis revealed considerable heterogeneity in the chronic lesions: some are 'closed' with no detectable extracellular water, but most are 'open' and show expansion of the extracellular space to as much as 87% of tissue area. This variable expansion probably results from differing degrees of axonal loss. Evidence of blood-brain barrier damage was found in only 17% of lesions, was less severe than that seen in acute lesions, and may result from repeated previous inflammatory insults. The findings imply progressive axonal loss in lesions as they age. It is possible that this loss is related to clinical progression of the disease.

INTRODUCTION

Pathological examination of the brain in multiple sclerosis (MS) usually reveals numerous chronic lesions characterized by complete demyelination and an excess of astrocytic processes. Evidence of active inflammation is occasionally seen at the margins of these lesions (Prineas and Connell, 1978), but is usually absent within them. While they are often referred to as 'burnt-out' plaques, there is pathological evidence to suggest that many of these lesions continue to show a disturbance of blood-brain barrier (BBB) function (Broman, 1964), and have a chronically expanded extracellular space (Périer and Grégoire, 1965).

The MS NMR research group at the National Hospital has undertaken parallel clinical and experimental studies designed to investigate the natural history and pathophysiological changes of the MS lesion. As part of this programme of research, a preliminary study was carried out 3 yrs ago which showed that many periventricular lesions known to have been at least 1 yr old displayed quantitative MRI properties similar to those of vasogenic oedema in which the extracellular space expands secondary to BBB damage: T_1 and T_2 were very prolonged, and the T_2 relaxation process was frequently biexponential (Barnes *et al.*, 1987). The possibility therefore arose that a BBB defect may persist in longstanding lesions and be of pathogenetic significance in the progression of the disease.

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Gadolinium-DTPA (Gd-DTPA) is a paramagnetic MRI contrast agent which identifies regions of abnormal BBB permeability by reducing local tissue T_1 values. These regions then enhance on T_1-weighted images. In the present study, quantitative and Gd-DTPA enhanced MRI have been used to investigate the relationship between changes in tissue spaces and BBB function in lesions identified in the original study, and known to be now at least 4 yrs old. We also describe the postmortem ultrastructural appearances of 4 chronic lesions from a different patient, and discuss them in relation to the MRI results.

METHODS

Electron microscopy

Two periventricular and 2 deep white matter lesion areas from the postmortem perfusion-fixed brain of a patient with longstanding definite MS were examined by transmission electron microscopy. A more detailed account of the method of fixation has been published elsewhere (Prineas, 1975). The size of the extracellular space in lesions was measured by planimetry. Micrographs (8×10 inch prints at ×4000 magnification) from the regions of interest were placed on a Summagraphics bit pad and an electronic pen was passed round the cell processes. A computed value for the proportion of the print occupied by extracellular space was calculated automatically. Five prints from randomly selected regions were examined from each lesion.

Patients

Sixteen patients with clinically definite MS (Poser *et al.*, 1983) volunteered for the study and provided informed consent. All had been examined by MRI both 3 and 4 yrs previously. There were 11 women and 5 men; mean age was 41 (range 30–79) yrs, and mean duration of disease was 15.6 (range 5–59) yrs. Four patients had stable MS, and 12 had slowly progressive symptoms (1 primary and 11 secondary progressive MS); none had suffered an acute clinical relapse in the previous 2 yrs. The project had National Hospital Ethics Committee approval.

Magnetic resonance imaging

MRI was performed on a Picker system operating at 0.5 tesla. The field of view was 30 cm, slice thickness 5 mm, and image matrix 128×256; pixel size was therefore 1.2×2.3×5 mm. A total of 53 lesions was selected for study, all of which had been present at the time of the previous MRIs. Each lesion was at least 5 mm in diameter, and visible on 3 continuous 5 mm slices of a multislice spin-echo pilot sequence (TE = 40 ms; TR = 500 ms). The middle slice was selected for study to minimize partial volume effects.

Two images (SE2000/40 and IR2000/500/40) were acquired from the selected anatomical plane for the generation of a T_1 calculated image using the manufacturer's two-point algorithm. A multiecho, modified Carr-Purcell-Meiboom-Gill (CPMG) sequence (TR = 2000 ms) consisting of 16 echoes at 40 ms intervals provided data for analysis of the T_2 relaxation characteristics. A detailed description of this analysis has been published previously (Barnes *et al.*, 1988). Briefly, signal intensity readings of lesions and normal-appearing white matter were taken direct from each image in the CPMG set. A least-squares fit was performed on these readings from all lesions to derive the best mono and biexponential functions. The monoexponential function yielded a T_2 value denoted as T_2' (in recognition of the fact that, in biexponential lesions, this value does not fully describe the T_2 relaxation process). T_1 and T_2' values were therefore derived for every lesion. In those lesions from which a biexponential function could be obtained, the improvement of fit over the monoexponential function was assessed from the ratio of the variances of the functions by means of an F test. T_2 relaxation was considered to be biexponential if the F statistic was significant at the 5% level. In those lesions which were found to be biexponential (but not the rest), 3 parameters were obtained from the least-squares fit; T_2 values for the fast (T_2 fast) and slow (T_2 slow) T_2 components, and the proportion of the total signal generated by the slow T_2 component (% T_2 slow).

Gd-DTPA was then given intravenously (0.1 mmol·kg^{1}), and the sequences repeated 4 times over the following hour. The presence or absence of enhancement in lesions was assessed independently by 2 observers

(D.B. and B.D.Y.), and from the calculated T_1 images the reduction in T_1 within enhancing lesions could be measured. The degree (percentage decreases in T_1) and timing of enhancement after Gd-DTPA was recorded from each lesion and from frontal normal-appearing white matter. The T_1, T_2', and T_2 relaxation characteristics of enhancing and nonenhancing lesion groups were compared using nonparametric (Mann-Whitney) analysis.

RESULTS

Ultrastructural appearances

Tissue preservation was satisfactory with no obvious artefactual damage. In particular, white matter distant from the lesions showed normal myelin morphology and tissue spaces, and blood vessels and their perivascular spaces were intact.

Each lesion showed abnormalities characteristic of longstanding MS plaques: axons were completely demyelinated and interspersed with a greatly increased number of astrocytic processes, the latter characterized by sheaths of glial fibrils within them. The size of the extracellular space varied from being unidentifiable in 1 lesion ('closed'), to being greatly expanded in the other 3 ('open') lesions (fig. 1), but extravasated serum protein was not seen. Planimetric measurement of the extracellular space in the open lesions gave a mean value of 69% (maximum 87%) of tissue area. The size of the extracellular space correlated with the degree of axonal loss, whereas glial processes were plentiful in all lesion areas. At the edges of the closed plaque, there was a sharp transition to normal-appearing white matter. By contrast, in the open lesions the extracellular space remained visibly expanded well beyond the margin of demyelination.

Many blood vessels within lesions were thickened and contained excessive collagen in their walls, changes well documented in chronic MS plaques (Weller, 1985). The endothelial lining, however, always appeared intact, and the endothelial cells themselves were morphologically normal. The perivascular space in normal-appearing white matter and closed lesions was small, but in open lesions, many vessels showed a widened perivascular space, sometimes containing macrophages.

Magnetic resonance imaging

A total of 53 lesions was studied. T_1 and T_2' values were increased compared with normal-appearing white matter in all lesions, but showed a wide range (fig. 2); T_1 varied from 594 to 1515 ms, and T_2' from 107 to 450 ms. The relaxation times from normal-appearing white matter and lesions are summarized in the Table.

The percentage change in the T_1 of normal-appearing white matter after Gd-DTPA ranged from −5 to 7.2. Of the 53 lesions, 9 were judged to show enhancement, and in these lesions the percentage decrease in T_1 ranged from 17 to 108, with a mean of 32. Of the other 44 lesions, none showed a change in T_1 of more than 10%. Only 1 enhancing lesion showed florid enhancement (108% decrease in T_1) on visual inspection of the images; in the other 8, it was much less obvious (fig. 3). Enhancement reached its maximum 15 min after Gd-DTPA in the brightly enhancing lesion, but was of more gradual onset, and occurred late in the remainder (30 min in 1, and 45 or 60 min in 7). There were no significant differences in T_1, T_2' or T_2 relaxation characteristics between the nonenhancing and enhancing groups of lesions.

In each patient, the T_2 relaxation process was monoexponential in normal-appearing

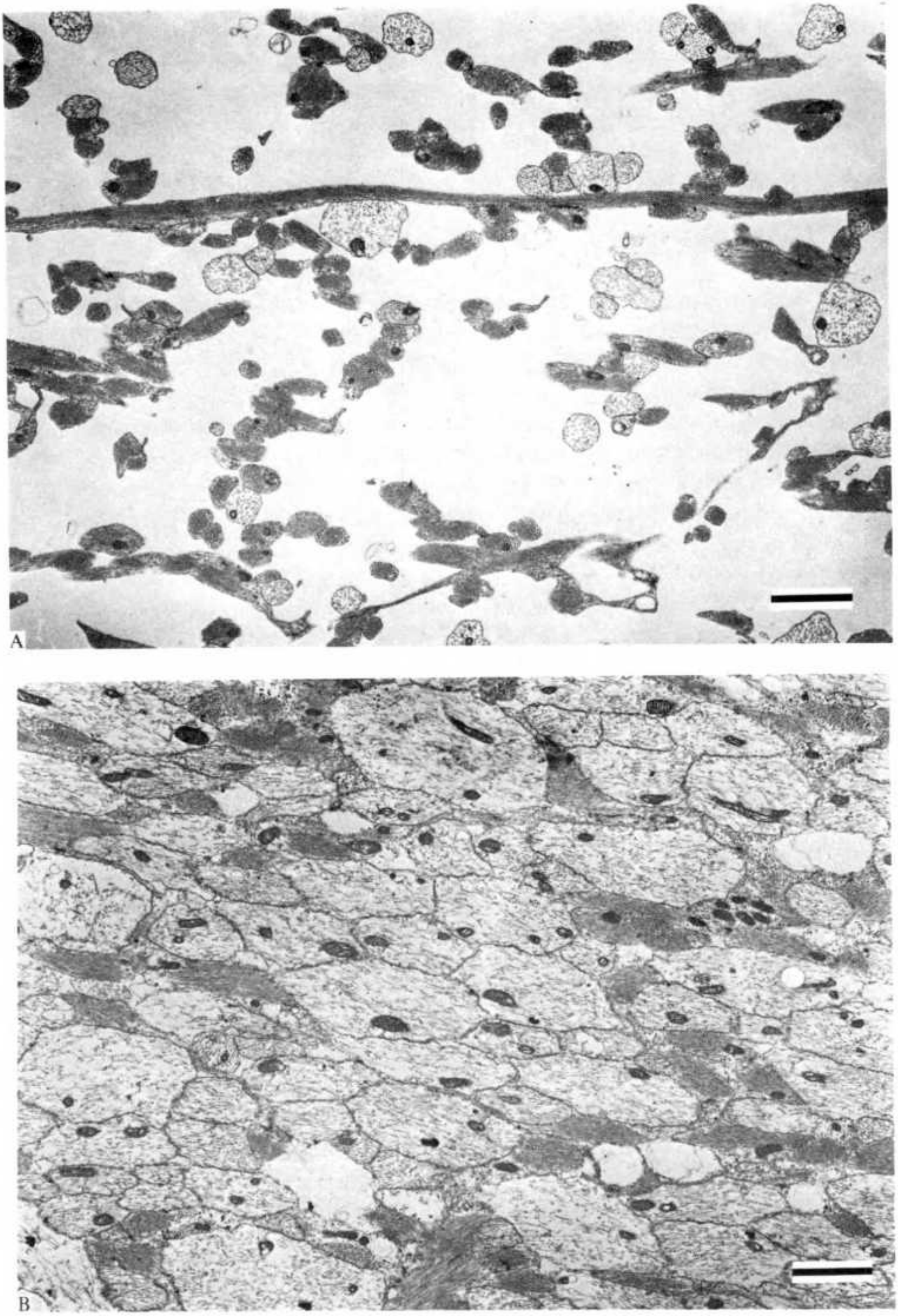

FIG. 1. Electron micrographs showing (A) 'open' and (B) 'closed' regions of longstanding multiple sclerosis lesions. Bars = 2 μm.

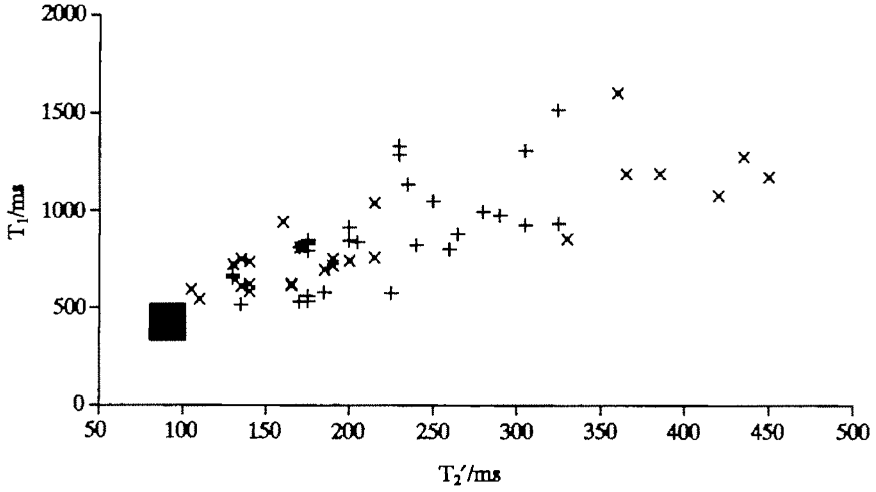

FIG. 2. Graph showing the range of T_1 and T_2' values for normal-appearing white matter (shaded box), and for individual mono (×) and biexponential (+) lesions.

TABLE THE RELAXATION TIMES OF NORMAL-APPEARING WHITE MATTER AND LESION GROUPS

Tissue type	*T_1 (ms)*	*T_2' (ms)*
White matter	430 (35)	85 (4.3)
All lesions (n = 53)	861 (260)	223 (86)
Nonenhancing lesions (n = 44)	866 (237)	230 (88)
Enhancing lesions (n = 9)	838 (349)	187 (75)

1 SD in brackets.

white matter. Of the 53 lesions studied, 28 showed significantly biexponential T_2 relaxation (fig. 2). Four of the 9 enhancing, and 24 of the 44 non-enhancing lesions were biexponential. Typical relaxation curves for normal-appearing white matter and a mono and biexponential lesion from a single patient are shown in fig. 4. The mean (1 SD) T_2fast and T_2slow were 84 (29) ms and 318 (182) ms, respectively, and % T_2slow ranged from 33 to 85 with a mean of 62. The distribution of the number of mono and biexponential lesions with respect to their T_2' values is shown in fig. 5. Interestingly, the monoexponential lesions showed a bimodal distribution, with low (peak A) and high (peak B) T_2 peaks around a central block of biexponential lesions.

DISCUSSION

The extracellular space

There was considerable variation in the size of the extracellular space in the 4 lesions examined by electron microscopy: in 1 it was not expanded, but in the other 3, regions

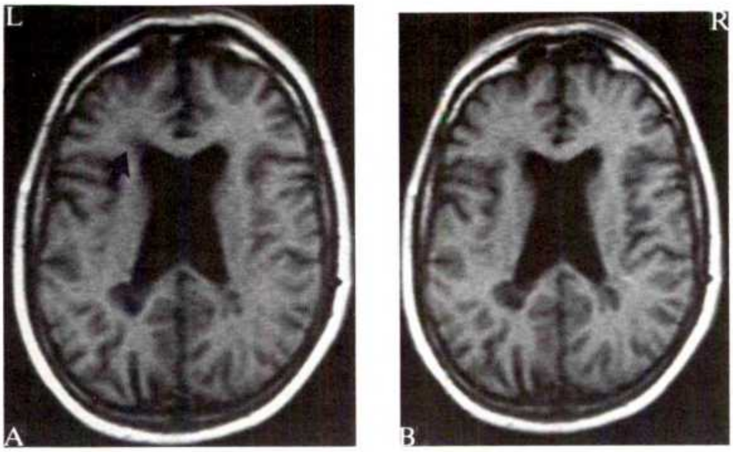

FIG. 3. A, pre- and B 1 h post-Gd-DTPA T_1-weighted images showing increase in signal (enhancement) in the arrowed lesion.

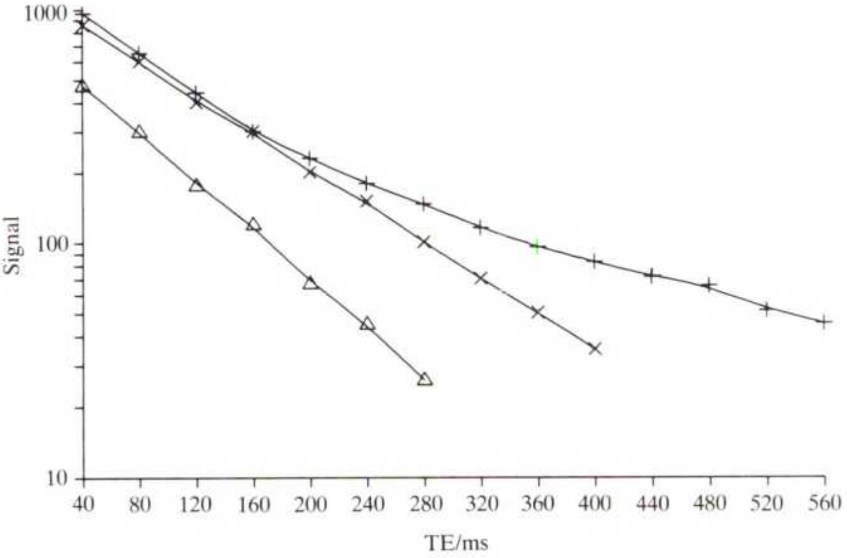

FIG. 4. Graph showing T_2 relaxation curves for normal-appearing white matter (triangles), and mono (×) and biexponential (+) lesions from 1 patient. The biexponential curve is characterized by a slowly relaxing component which prolongs the decay of signal with echo time (TE).

of expanded extracellular space occupying up to 87% of section area were seen. In the latter open lesions, the most striking correlation was with a marked reduction in axonal density relative to the number of glial processes. These findings correspond closely to the appearances following immersion-fixation described by Périer and Grégoire in 1965, and probably explain the 'spongy' consistency of periventricular lesions in unfixed brain at postmortem.

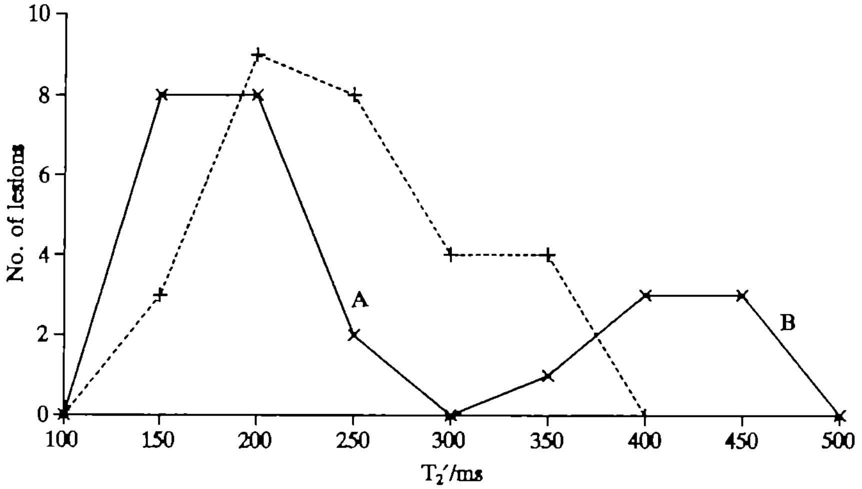

FIG. 5. Graph showing the distribution of the number of mono (×) and biexponential (+) lesions with respect to their T_2' values. The monoexponential lesions show separate low (A) and high (B) T_2' peaks.

Experimental in vivo studies have shown that the MRI characteristics of an expanded extracellular space are marked prolongation of T_1 and T_2' with biexponential T_2 relaxation; T_2fast (intracellular water) is <100 ms and T_2slow (water in the extracellular space) is >200 ms (Naruse *et al.*, 1982; Barnes *et al.*, 1987; Castro *et al.*, 1987). These characteristics were found in 28/53 lesions in the present study, and similar findings have been reported by others (Larsson *et al.*, 1988; Rumbach *et al.*, 1988; Gounot *et al.*, 1989). The wide range of T_1 and T_2' values implies a similarly wide range of pathological appearances as was observed ultrastructurally. Our mean T_2fast (84 ms) and T_2slow (318 ms) values in MS lesions agreed closely with those of Rumbach *et al.* (1988) who measured T_2fast at 86 ms and T_2slow at >280 ms, values compatible with intracellular and extracellular water, respectively. Furthermore, the mean percentage T_2slow, from extracellular water, of 62% was similar to the mean extracellular space size of 69% measured in the post-mortem specimens.

Although we found only 28 lesions to be biexponential, fig. 5 shows 2 peaks of monoexponential lesions, peak B containing 7 with very high T_2' values (2 enhancing, 5 nonenhancing) suggesting that in these lesions the extracellular space was so expanded that any MRI signal from intracellular water could not be resolved as a separate component. If that is accepted, there was therefore MRI evidence for an expanded extracellular space in a total of 35/53 lesions (66%). It is worth noting that gliosis alone does not prolong T_2' (Parrish *et al.*, 1974) or produce biexponential T_2 relaxation (Barnes *et al.*, 1988) and cannot be responsible for the MRI characteristics of the majority of longstanding lesions.

Although our morphological results are from a single case, the findings are compatible with all available MRI data from both experimental models of extracellular space expansion and clinical studies of MS as discussed above. Clearly the residual lesions in the MS brain are heterogeneous, but the relationship between different types of lesion and the resultant functional derangement is unclear. It is obvious that the potential for recovery after axonal loss must be less than after pure demyelination. The next step will be to determine whether and how often closed lesions transform in open ones, and whether such change corresponds with the development of a fixed deficit.

The blood-brain barrier

Serial studies with contrast-enhanced MRI have confirmed that 90% of new lesions in relapsing-remitting and secondary progressive MS are associated with breakdown of the BBB (Gonzalez-Scarano *et al.*, 1987; Kermode *et al.*, 1990; A. J. Thompson, unpublished data). The dynamics of Gd-DTPA enhancement have provided insight into both the duration (Miller *et al.*, 1988; Thompson *et al.*, 1989) and severity of the BBB disturbance (Kermode *et al.*, 1990). New lesions enhance brightly within 5 min of Gd-DTPA administration and measured T_1 values usually fall by 100% or more as a result of egress of the substance from the circulation into the lesions. Experimental studies have shown that enhancement is due exclusively to the influence of Gd-DTPA on extracellular water (Braunschweiger *et al.*, 1986). Furthermore, analogous studies of experimental allergic encephalomyelitis indicate that this type of enhancement is always associated with inflammation (Hawkins *et al.*, 1990).

What has not been determined with certainty from imaging studies in MS is whether a more subtle BBB defect exists in longstanding lesions. In the present study we found a slow, modest pattern of enhancement in 8/53 lesions, distinct from the type seen in acute lesions, but similar to that previously reported in demyelinating cervical cord lesions by Larsson *et al.* (1989). It was also noted in the brain in clinically stable MS by Gonzalez-Scarano (1987), who postulated that a different pathophysiological basis for the BBB disturbance from that in acute lesions may be responsible. We concur with this view for which there is also support from microscopic (Broman, 1964) and CSF studies (Walker *et al.*, 1985). The type of enhancement seen in our 8 lesions may reflect a non-inflammatory BBB defect resulting from incomplete repair following repeated previous inflammatory insults.

But is the expanded extracellular space in longstanding MS lesions due to a BBB disturbance of the kind seen in vasogenic oedema? The present study suggests not, because first, there was no difference in the quantitative MRI characteristics between the groups of enhancing and nonenhancing lesions, and secondly, the majority of biexponential lesions did not enhance. The ultrastructural findings suggest that in most lesions, the extracellular space (including the perivascular space) expands secondary to axonal loss.

In summary, longstanding MS lesions show considerable pathological and MRI heterogeneity. Some lesions are closed, but in about two-thirds the extracellular space is pathologically expanded, probably secondary to axonal loss. About one-fifth of lesions show a BBB defect to Gd-DTPA which is dynamically distinct from that seen in acute, inflammatory lesions, and which may result from incomplete repair following recurrent BBB damage (Koopmans *et al.*, 1989; Hawkins *et al.*, 1990) in the course of lesion development. The significance of these observations in relation to the pathological and clinical progression of the disease will remain unclear until the results of serial studies become available. If, as has been suggested, blood-borne disease mediators such as complement are important in MS (Morgan *et al.*, 1984; Scolding *et al.*, 1989), then a chronic BBB defect of the kind we have observed might allow such mediators to diffuse through open lesions and promote new inflammation at their myelinated margins, as is commonly seen both pathologically (Prineas and Connell, 1978) and on MRI (Miller *et al.*, 1988). These MRI techniques should provide a sensitive method for the long-term assessment of treatments aimed at retarding disease progression.

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REFERENCES

BARNES D, McDONALD WI, JOHNSON G, TOFTS PS, LANDON DN (1987) Quantitative nuclear magnetic resonance imaging: characterisation of experimental cerebral oedema. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 125–133.

BARNES D, McDONALD WI, LANDON DN, JOHNSON G (1988) The characterization of experimental gliosis by quantitative nuclear magnetic resonance imaging. *Brain*, **111**, 83–94.

BRAUNSCHWEIGER PG, SCHIFFER LM, FURMANSKI P (1986) ^{1}H-NMR relaxation times and water compartmentalization in experimental tumor models. *Magnetic Resonance Imaging*, **4**, 335–342.

BROMAN T (1964) Blood-brain barrier damage in multiple sclerosis: supravital test-observations. *Acta Neurologica Scandinavica*, **40**, Supplement 10, 21–24.

CASTRO ME, TREIBER EO, LUNT JA, BOISVERT DPJ, ALLEN PS (1987) Comparison of in-vivo and in-vitro R2 of protons in cats with experimental brain edema. *Sixth Annual Society of Magnetic Resonance in Medicine Meeting*, Abstract 715.

GONZALEZ-SCARANO F, GROSSMAN RI, GALETTA, S, ATLAS SW, SILBERBERG DH (1987) Mutiple sclerosis disease activity correlates with gadolinium-enhanced magnetic resonance imaging. *Annals of Neurology*, **21**, 300–306.

GOUNOT D, ARMSPACH JP, RUMBACH L, CHAMBRON J (1989) Quantitative analysis of multiple sclerosis in clinical MRI. *Eighth Annual Society of Magnetic Resonance in Medicine Meeting*, Abstract 726.

HAWKINS CP, MUNRO PMG, MACKENZIE F, KESSELRING J, TOFTS PS, DU BOULAY EPGH *et al.* (1990) Duration and selectivity of blood-brain barrier breakdown in chronic relapsing experimental allergic encephalomyelitis studied by gadolinium-DTPA and protein markers. *Brain*, **113**, 365–378.

KERMODE AG, TOFTS PS, THOMPSON AJ, MACMANUS DG, RUDGE P, KENDALL BE *et al.* (1990) Heterogeneity of blood-brain barrier changes in multiple sclerosis: an MRI study with gadolinium-DTPA enhancement. *Neurology, Cleveland*, **40**, 229–235.

KOOPMANS RA, LI DKB, OGER JJF, MAYO J, PATY DW (1989) The lesion of multiple sclerosis: imaging of acute and chronic stages. *Neurology, Cleveland*, **39**, 959–963.

LARSSON E-M, HOLTÅS S, NILSSON O (1989) Gd-DTPA–enhanced MR of suspected spinal multiple sclerosis. *American Journal of Neuroradiology*, **10**, 1071–1076.

LARSSON HBW, FREDERIKSEN J, KJAER L, HENRIKSEN O, OLESEN J (1988) *In vivo* determination of T1 and T2 in the brain of patients with severe but stable multiple sclerosis. *Magnetic Resonance in Medicine*, **7**, 43–55.

MILLER DH, RUDGE P, JOHNSON G, KENDALL BE, MACMANUS DG, MOSELEY IF *et al.* (1988) Serial gadolinium enhanced magnetic resonance imaging in multiple sclerosis. *Brain*, **111**, 927–939.

MORGAN BP, CAMPBELL AK, COMPSTON DAS (1984) Terminal component of complement (C9) in cerebrospinal fluid of patients with multiple sclerosis. *Lancet*, **ii**, 251–255.

NARUSE S, HORIKAWA Y, TANAKA C, HIRAKAWA K, NISHIKAWA H, YOSHIZAKI K (1982) Proton nuclear magnetic resonance studies on brain edema. *Journal of Neurosurgery*, **56**, 747–752.

PARRISH RG, KURLAND RJ, JANESE WW, BAKAY L (1974) Proton relaxation rates of water in brain and brain tumors. *Science*, **183**, 438–439.

PÉRIER O, GRÉGOIRE A (1965) Electron microscopic features of multiple sclerosis lesions. *Brain*, **88**, 937–952.

POSER CM, PATY DW, SCHEINBERG L, MCDONALD WI, DAVIS FA, EBERS GC *et al.* (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, **13**, 227–231.

PRINEAS J (1975) Pathology of the early lesion in multiple sclerosis. *Human Pathology*, **6**, 531–554.

PRINEAS JW, CONNELL F (1978) The fine structure of chronically active multiple sclerosis plaques. *Neurology, New York*, **28**, Supplement, 68–75.

RUMBACH L, SELLAL F, CHAMBRON J, WARTER JM, COLLARD M (1988) MRI and T2 relaxation time measurement in multiple sclerosis brain lesions. *Journal of Neurology*, **235**, Supplement S91–S92.

SCOLDING NJ, MORGAN BP, HOUSTON A, CAMPBELL AK, LININGTON C, COMPSTON DAS (1989) Normal rat serum cytotoxicity against syngeneic oligodendrocytes: complement activation and attack in the absence of anti-myelin antibodies. *Journal of the Neurological Sciences*, **89**, 289–300.

THOMPSON AJ, KERMODE AG, MACMANUS DG, KINGSLEY DPE, KENDALL BE, MOSELEY IF *et al.* (1989) Pathogenesis of progressive multiple sclerosis. *Lancet*, **i**, 1322–1323.

WALKER RWH, THOMPSON EJ, MCDONALD WI (1985) Cerebrospinal fluid in multiple sclerosis: relationships between immunoglobulins, leucocytes and clinical features. *Journal of Neurology*, **232**, 250–259.

WELLER RO (1985) Pathology of multiple sclerosis. In: *McAlpine's Multiple Sclerosis*. Edited by W. B. Matthews, E. D. Acheson, J. R. Batchelor and R. O. Weller. Edinburgh: Churchill Livingstone, pp. 301–343.

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SYMPATHETIC MUSCLE NERVE ACTIVITY DURING SLEEP IN MAN

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SUMMARY

Muscle sympathetic activity (MSA) was recorded in the peroneal nerve during sleep in 14 sleep-deprived healthy subjects. Continuous noninvasive recordings of finger blood pressure were obtained in 7 subjects. In light sleep (stage 2 sleep) the number of sympathetic bursts/min decreased to 90±8% (mean±SEM) and total MSA (= burst/min×mean burst area) to 89±5% of the awake value ($P < 0.05$, n = 14). In deep sleep (stage 3–4) total MSA decreased further, to 71±8% of the awake value (n = 5). There was no close correlation between variations of depth of sleep and variations of sympathetic activity but during continuously deepening sleep MSA decreased progressively with time. In stage 2 sleep, high amplitude K complexes were accompanied by short-lasting increases of sympathetic activity. Since these increases of MSA were not preceded by decreases of diastolic blood pressure, which is known to evoke increased sympathetic nerve traffic in muscle nerves, we suggest that K complex related increases of MSA are signs of arousal which elicit both cortical EEG phenomena and activation of cerebral sympathetic centres. During desynchronized (REM) sleep, total MSA increased to 124±12% of the value in awake state (n = 5). The increases occurred mainly in short irregular periods, often related to rapid eye movements and there was an inverse relationship between the duration of the desynchronized sleep and the increase of total MSA. Our findings are similar to the data obtained in animal experiments and may partly explain changes of blood pressure during synchronized and desynchronized sleep reported previously in man.

INTRODUCTION

Sleep is accompanied by changes of cardiovascular functions. During synchronized (non-REM) sleep, blood pressure, cardiac output, total peripheral resistance and heart rate have been found to decrease in many species (for references *see* Mancia and Zanchetti, 1980; Coote, 1982). During desynchronized sleep a further (tonic) fall of blood pressure was reported in the majority of investigated species (although a slight increase was found in the rat) but often interrupted by irregular short-lasting (phasic) blood pressure increases. In mammals, heart rate also became variable during desynchronized sleep with bradycardia interrupted by considerable tachycardic swings (*see*, e.g., Gassel *et al.*, 1964; Guazzi and Zanchetti, 1965; Mancia *et al.*, 1971). In man, heart rate and blood pressure increased slightly during desynchronized (REM) sleep (Khatri and Freis, 1967) and displayed large variations (Snyder *et al.*, 1964; Coccagna *et al.*, 1971).

Several attempts have been made to clarify the mechanisms underlying cardiovascular changes during sleep. Since variations of blood pressure are influenced by sympathetic nerves supplying resistance vessels, sympathetic activity to different vascular beds has

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been recorded in animals. During synchronized sleep, renal sympathetic nerve traffic decreased in the cat (Baust *et al.*, 1968). In desynchronized (REM) sleep, mean activity decreased in renal and splanchnic sympathetic fibres but increased in muscle sympathetic fibres. During this sleep stage the variability of sympathetic activity in all nerves was much higher because of short-lasting marked increases of sympathetic traffic (Coote and Futuro Neto, 1981; Coote, 1982).

In man, sympathetic activity has not been recorded during sleep. In the awake state the microneurographic technique has been used extensively for measurements of sympathetic outflow to skeletal muscles. Such recordings have shown that muscle sympathetic activity (MSA) is involved in blood pressure homeostasis. The sympathetic muscle nerve traffic is composed of bursts of vasoconstrictor impulses synchronous with the heart beat (Delius *et al.*, 1972; Wallin and Fagius, 1988). The bursts occur predominantly during transient reductions of blood pressure and are normally not influenced by arousal or short-lasting emotional stimuli.

The present study deals with human MSA during spontaneous sleep. The aim was to investigate whether the cardiovascular changes mentioned above have a counterpart in sympathetic outflow to muscles. To this end we recorded MSA (and in some experiments arterial blood pressure) during different sleep stages in healthy volunteers.

METHODS

Experiments were performed on 21 healthy subjects, 4 males and 17 females aged 23–53 (mean 34) yrs who had not slept for more than 2–3 h during the night before the experiment. The study was approved by the local Ethics Committee and the subjects gave their informed consent. Experiments in which subjects only reached stage 1 sleep (4 cases) or just a few minutes of stage 2 sleep (3 cases) were excluded from the analysis. The 14 experiments included in the analysis were conducted mostly in the afternoon (11 subjects), in 2 cases in the morning and in 1 case in the evening.

The following parameters were recorded: 13 bipolar EEG derivations from the frontotemporal, temporocentral, temporotemporal, temporo-occipital, centroparietal, parieto-occipital and the Fz-Cz regions; a submental electromyogram (EMG); an electro-oculogram (EOG) by electrodes at the outer canthi; electrocardiogram (ECG) by precordial surface electrodes; respiratory movements by a strain gauge attached around the chest with a rubber strap; muscle sympathetic nerve activity (*see below*) and blood pressure (*see below*). Analogue signals of all parameters were stored on a 16-channel tape-recorder (V-Store, Racal, Southampton, UK) and, in addition, all signals were displayed on a 21-channel ink jet recorder (Siemens-Elema, Solna, Sweden) mostly with a paper speed of 15 $\mathrm{mm \cdot s^{-1}}$.

Recording of sympathetic nerve activity

Intraneural recordings of multiunit sympathetic activity were made in the peroneal nerve at the fibular head with tungsten microelectrodes having uninsulated tips of a few μm. The signals were amplified with a total gain of 50 000 and passed through a bandpass filter (bandwidth 0.7–2 kHz) and an amplitude discriminator to improve the signal-to-noise ratio. An RC-integrating network (time constant 0.1 s) was used to obtain a mean voltage neurogram. Muscle nerve sympathetic activity (MSA) was identified according to the following criteria: (1) weak electrical stimulation through the recording electrode evoked muscle twitches without concomitant skin paraesthesiae; (2) tapping on the muscle belly or passive stretching of the muscle gave rise to afferent mechanoreceptive activity; and (3) light skin touches did not evoke afferent activity. Evidence that MSA is composed of sympathetic vasoconstrictor impulses and details of the recording technique have been described previously (Delius *et al.*, 1972; Sundlöf and Wallin, 1977).

Measurement of blood pressure

Blood pressure was measured continuously on a finger by a device based on the volume-clamp principle (Yamakoshi *et al.*, 1988). The instrument clamps the volume of the finger, measured by infrared plethysmography, at a value where arteries experience zero transmural pressure. This is done by a servoloop-controlled hydraulic finger constriction cuff which, as a consequence, develops a pressure which closely follows the intra-arterial pressure and which may be used as a continuous indirect measure of blood pressure (Cejnar *et al.*, 1988). Unfortunately, a periodic cuff readjustment procedure (every 100–500 heart beats) necessary for accurate blood pressure measurement tended to arouse the subjects and therefore blood pressure was measured only in the first 7 experiments (*see* Table).

Experimental procedure

Subjects were lying in a comfortable supine position at a room temperature of 22–25° C. After placing the EEG, EMG, EOG and ECG electrodes and the strain gauge around the chest, the recording electrode was inserted in the peroneal nerve. When a suitable recording site was found, resting awake MSA was recorded for 10 min and then subjects were encouraged to go to sleep. If the nerve recording site deteriorated within the first 45–60 min, small adjustments were made and after a 5 min awake period subjects were allowed to go to sleep again. Experiments were terminated after 90–120 min of sleep or when the recording site was lost.

In 2 experiments the intraneural position of the recording electrode changed during sleep due to leg movements; in both cases REM sleep occurred after the change. In these 2 experiments only the recording after the change of the position of the electrode was analysed, the awake or stage 1 periods following the movements were taken as 'awake' values. In 2 other experiments limb movements made the nerve recording unreliable during the second part of the experiments; in these cases we included only the initial part of the experiment (before movement artefacts) in the analysis.

Analysis

Sleep stages were scored by 2 investigators throughout the whole record in 1 min epochs according to the criteria of Rechtschaffen and Kales (1968). Spectral EEG analysis was made with a computer-aided method using the parieto-occipital EEG derivations (Matousek and Petersén, 1983). For statistical analysis the relative power (in %) within the frequency bands of 1.5–7.5 Hz (delta and theta waves) and 7.5–12.5 Hz (alpha waves) were calculated.

Muscle sympathetic activity was analysed using a computer program (M. Cejnar, F. Goethe, M. Hornyak, B. G. Wallin, unpublished). The program emulates the manual analysis by detecting each MSA burst in the mean voltage neurogram and calculating its area. In this procedure mean voltage neurogram, ECG and time code were digitized off-line at 200 Hz using a DataTranslation (DT-2851) analogue-to-digital interface card. A sympathetic burst was identified on the basis of a monotonic rise and fall with a local maximum occurring in a smoothed MSA signal within 1000–1800 ms from the preceding R wave in the ECG signal. Most of the parameters defining a burst could be changed manually, for example, the tolerance limits of the skewness of the rising or falling parts, the latency of the peak of the burst from the R wave and the minimum height of bursts, respectively. Artefacts were rejected on the basis of having short rise time and/or duration (less than 0.17 s). The area of a burst was calculated on a relative baseline (mean value of background activity between bursts). The digitized mean voltage neurogram and the identified bursts were displayed together on an ink jet recorder via two digital-to-analogue converters and if the automatically detected bursts did not agree with the visually defined ones, parameters were changed and the automatic burst detection was restarted. Artefacts falsely identified as bursts occurred seldomly and were eliminated by manual editing of the burst record. Values of nerve activity, R-R interval, sympathetic reflex latency and systolic, mean and diastolic blood pressures were evaluated for each heart period and stored. Sympathetic reflex latency for the inhibitory baroreflex was measured from the R wave of the ECG to the peak of the corresponding burst in the mean voltage neurogram, the peak being taken as the start of inhibition induced by the systolic pressure wave (for details, *see* Fagius and Wallin, 1980). Finally, for each minute the computer calculated the number of sympathetic bursts, total MSA (number of bursts × mean burst area) and mean values of sympathetic reflex latency, R-R interval, systolic, diastolic and mean blood pressure.

In stage 2 sleep, additional analysis of MSA was made when a K complex in the EEG recording occurred. A K complex was selected for analysis.if it lasted more than 0.5 s, was extensively distributed, started with a well defined, high-amplitude (more than 10 μV) sharp-wave and was not followed by another K complex within 4–6 s (*see also* fig. 4). In all subjects MSA was compared between two 4 s periods, one immediately preceding and one immediately following the peak of the first sharp-wave of a K complex.

Furthermore, in 6 subjects in whom blood pressure was recorded in stage 2 sleep MSA, cardiac interval, and diastolic blood pressure were analysed for each cardiac cycle starting 4 cardiac cycles before and ending 8 cycles after the peak of the first sharp-wave of the K complex.

Statistical analysis

For statistical comparisons of MSA between different sleep stages, 5 min sections of stage 2 sleep, regardless of the numbers of K complexes occurring in these sections, and stage 3–4 were analysed (in the stable phase of the first occurrence of the sleep stage). The results were compared with 5 min periods of the awake state usually taken from the awake period before sleep (in 2 cases following sleep, and in another 2 cases after an arousal causing limb movements and change of the recording site) even if in some cases the EEG record already showed signs of drowsiness (stage 1). This was justified by the finding that MSA values in the awake stage and in stage 1 did not differ (*see* Results).

For statistical analysis Wilcoxon's pair-matched sign-ranked test was used. Statistical tests were performed with the SPSS-PC+ statistical package (Version 2.0; SPSS Inc., USA). Results are expressed as mean ± SEM. *P* values less than 0.05 were considered as significant.

RESULTS

In general, there was good agreement between the visual scoring of sleep stages and the results of the spectral analysis of the EEG (fig. 2B). The normal temporal pattern of MSA did not change during sleep (fig. 1). Thus in all sleep stages there were still irregular sequences of sympathetic bursts which occurred predominantly during temporary blood pressure reductions (*cf* Delius *et al.*, 1972). The baroreflex latencies also remained constant (awake: 1.37 s, sleep stage 2: 1.37 s, sleep stage 3–4: 1.35 s and desynchronized (REM) sleep: 1.35 s). The EEG analysis showed that already during the initial 'awake' period some subjects reached sleep stage 1 (drowsiness). When true awake periods were compared with periods of drowsiness the strength of sympathetic activity did not differ significantly (total MSA during drowsiness was 97 ± 18% of the awake value, $P = 0.46$, $n = 6$). Therefore, MSA values from the awake period were accepted even if they also contained data from stage 1.

Synchronized (non-REM) sleep

Fourteen subjects reached stage 2 sleep (light sleep) and 5 subjects stage 3–4 (deep sleep, *see* Table). With increasing depth of sleep MSA decreased successively and in stage 2 the number of bursts/min was 90 ± 8% and total MSA was 89 ± 5% of the value in the awake state ($P < 0.05$ for both). In the 5 subjects who reached deep sleep (stage 3–4), total MSA decreased to 71 ± 8% from 81 ± 8% in stage 2 (a further decrease in 4 and unchanged activity in 1 subject). Examples of MSA records in different sleep stages in one subject are shown in fig. 1 and quantitative data from all subjects are summarized in fig. 2A and the Table. There was no close correlation with variations of depth of sleep, yet when total MSA was measured during consecutive 1 min periods during continuously deepening sleep MSA decreased progressively with time ($P < 0.001$ in 4 and $P = 0.10$ in 1 subject). An example of this relationship is shown in fig. 3. In stage 3–4, changes of total MSA were fairly consistent but in stage 2 there were more variations. To exclude a bias in the selection of 5 min periods we also analysed the whole period of stage 2 sleep in all subjects. The result was similar, that is, a decrease of the number of bursts/min to 92 ± 8% and a decrease of total MSA to 79 ± 10% of the awake value. When comparing total MSA between the first and last 5 min periods of stage 2 (mean duration: 14 min, range: 5–31 min), there was no change in 9 subjects

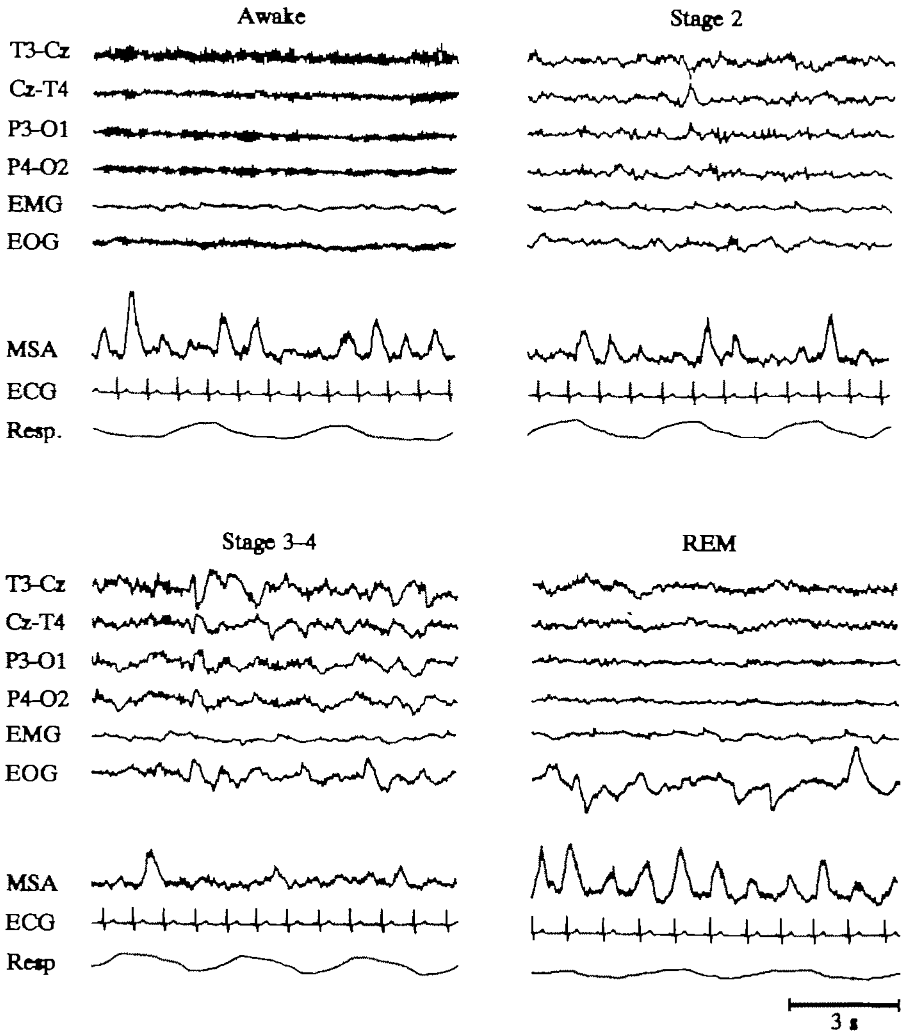

FIG. 1 Polygraphic recording in one subject (N.E.) during sleep. With increasing depth of sleep, muscle sympathetic activity (MSA) decreases. During rapid eye movements (REM) in desynchronized sleep a marked increase of MSA occurs. In stage 2 and stage 3–4 EEG artefacts appear in the EOG signal. Traces from above: EEG derivations (T3-Cz, Cz-T4, P3-O1, P4-O2), electromyogram (EMG), electro-oculogram (EOG), muscle sympathetic activity (MSA), electrocardiogram (ECG) and respiratory movements (Resp.).

but in 5 subjects total MSA was markedly lower at the end of stage 2 which accounts for the difference between the analysis of the whole stage 2 and of the selected 5 min periods.

Blood pressure did not change between the awake state and stage 2 sleep (n = 7). Heart rate was 67.2 ± 2.9 min^{-1} in the awake state, decreasing significantly to 63.4 ± 2.8 min^{-1} during stage 2 sleep (n = 14, P = 0.02) and to 65.1 ± 3.3 min^{-1} in stage 3–4 sleep (n = 5).

TABLE SUMMARY OF DATA FROM ALL SUBJECTS*

		Awake			*Stage 2*				*Stage 3–4*				*Desynchronized (REM) sleep*			
Subject	*Age (yrs)*	*Bursts* min^{-1}	*BP*	*Heart rate*	*Bursts* min^{-1}	*Total MSA % of awake*	*BP*	*Heart rate*	*Bursts* min^{-1}	*Total MSA % of awake*	*BP*	*Heart rate*	*Bursts* min^{-1}	*Total MSA % of awake*	*BP*	*Heart rate*
C.M.	31	25	131/83	61	19	99	133/83	53	–	–	–	–	–	–	–	–
S.K.	25	35	147/82	96	33	118	148/76	86	–	–	–	–	–	–	–	–
B.O.	35	26	134/73	56	18	51	136/75	61	17	41	136/76	62	34	170	135/73	59
N.E.	42	58	113/72	72	55	88	114/70	68	56	88	102/63	68	59	104	108/67	68
G.P.	25	29	123/73	60	25	88	127/71	55	–	–	–	–	–	–	–	–
J.G.	32	42	–	75	39	81	–	71	–	–	–	–	–	–	–	–
R.E.	26	20	120/78	54	19	98	136/84	50	–	–	–	–	–	–	–	–
G.M.	53	42	137/75	70	40	120	131/70	69	–	–	–	–	–	–	–	–
E U.	37	32	–	75	28	102	–	64	27	78	–	65	–	–	–	–
B.L.	31	33	–	58	33	80	–	53	32	71	–	55	41	107	–	60
B.A.	49	39	–	73	33	83	–	75	33	78	–	75	41	122	–	78
S A	39	38	–	65	39	103	–	62	–	–	–	–	–	–	–	–
H.K.	44	56	–	66	51	72	–	69	–	–	–	–	–	–	–	–
F.U.	24	33	–	61	25	65	–	52	–	–	–	–	33	120	–	57
Mean	35	36	129/77	67	33	89	132/76	63	33	71	119/70	65	42	124	122/70	64
SEM	2.5	2.9	4/2	2.9	3.1	5	4/2	2.8	6.4	8.0	–	3.3	4.7	12	–	3.9

* Total muscle sympathetic activity (MSA) is expressed as a percentage of the awake value. Blood pressure (BP) and heart rate values are given in mmHg and min^{-1}, respectively.

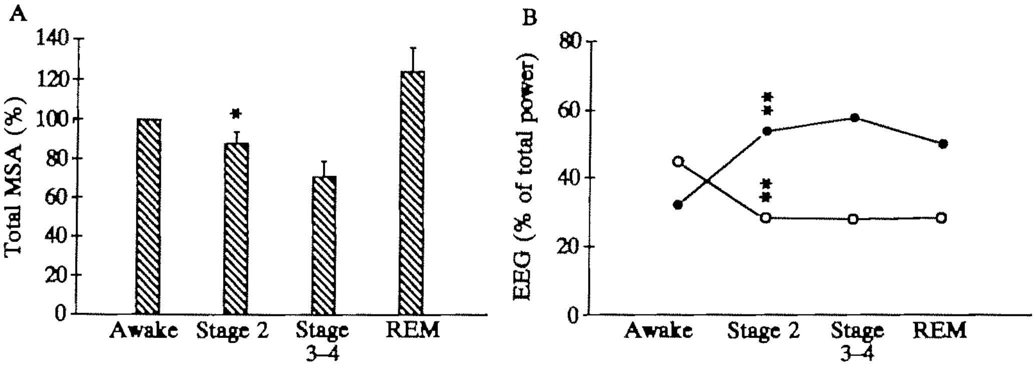

FIG. 2. Total muscle sympathetic activity (MSA) and EEG activity in 5 min periods of sleep stage 2, stage 3−4 and during the whole period of desynchronized (REM) sleep (mean duration: 7.4 min). A, MSA is expressed as a percentage of the awake value. B, percentage of total power of the frequency bands of 1.5−7.5 Hz (theta and delta waves, filled circles) and of 7.5−12.5 Hz (alpha waves, open circles) in the parieto-occipital EEG derivations. Significant differences from awake: *$P < 0.05$; **$P < 0.01$. Number of observations: n = 14 in the awake state and stage 2; n = 5 in stage 3−4 and in desynchronized (REM) sleep.

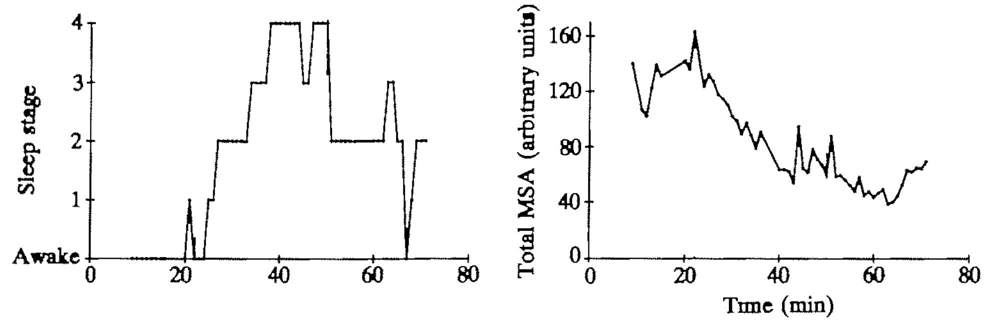

FIG. 3 Gradual fall of total muscle sympathetic activity (MSA) during sleep (subject N.E) MSA and sleep stages were analysed in 1 min periods. During the period of continuously deepening sleep, indicated by dotted lines, MSA decreased progressively with time ($P < 0.001$).

Relation of MSA to K complexes. In stage 2 sleep, high amplitude K complexes were accompanied by short-lasting increases of MSA (*see* fig. 4 and stage 2 sleep in fig. 1). For quantitative analysis 8−25 (mean 20) spontaneously occurring K complexes from 12 experiments met the criteria described in the Methods section (2 experiments were excluded because of the small number of K complexes meeting the criteria). Total MSA measured during the first 4 s after the first sharp-wave peak of the K complexes was significantly higher than total MSA during the 4 s preceding the K complexes (52 ± 7 vs 33 ± 5, arbitrary units; $P < 0.01$, n = 12). When compared during the same 4 s periods, heart rate was also higher after the K complex (64.2 ± 2.9 min^{-1} vs 61.2 ± 2.9 min^{-1}, $P < 0.01$, n = 12).

Blood pressure was recorded in 6 of the 12 experiments. In these cases, analysis of total MSA, R-R interval and diastolic blood pressure was made for each heart beat to

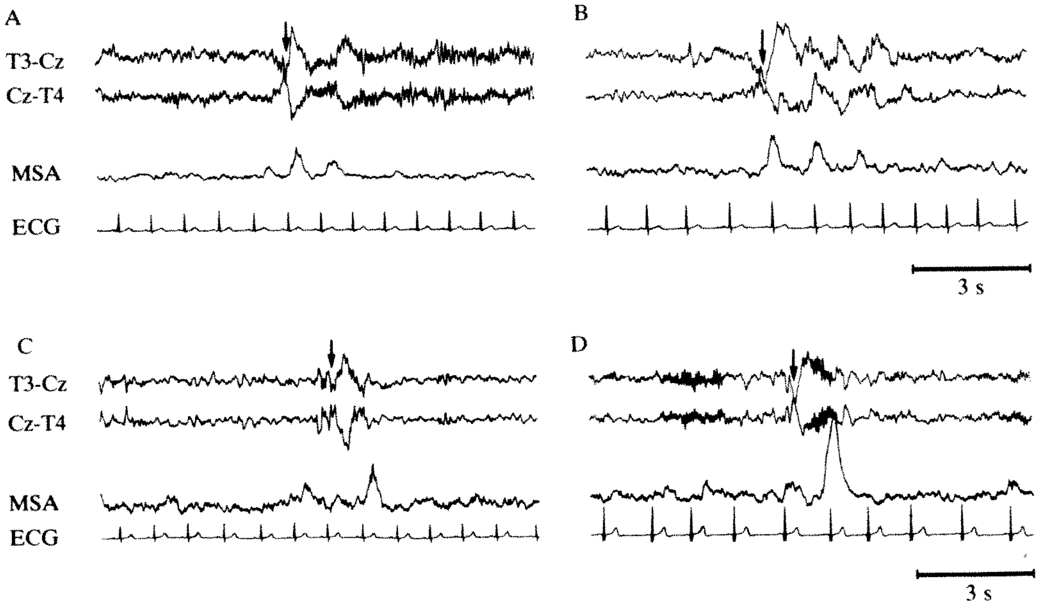

FIG. 4. Polygraphic recordings in 4 subjects (A, B, C, D) showing simultaneously appearing spontaneous K complexes and increases in muscle sympathetic activity (MSA) in stage 2 sleep. Arrows indicate the peak of the first sharp-wave of a K complex defined for the statistical analysis. For selection criteria of K complexes, *see* Methods. Abbreviations as in fig. 1.

reveal the exact time relationship between these parameters. MSA increased suddenly to a maximum during the second heart beat following the K complex (fig. 5). After the peak, MSA fell successively to values below the control level and at the sixth heart beat after the K complex, MSA was significantly less than the control, that is, the value during the cardiac cycle immediately preceding the K complex. The change of instantaneous heart rate occurred slightly later with a maximal value at the third heart beat whereas diastolic blood pressure reached its peak value 4 heart beats later than MSA (sixth heart beat from the K complex). Peak values of all 3 parameters were significantly different from the control values ($P < 0.05$).

Desynchronized (REM) sleep

Desynchronized sleep occurred in 5 subjects. Since its duration varied widely (mean 7.4, range 2–13.5 min), the whole period was analysed in all subjects. A record is shown in fig. 1.

During desynchronized sleep, total MSA increased to a mean of 124 ± 12% of the awake value (fig. 2A). The increases occurred mainly in short (10–30 s), irregular periods of high amplitude bursts. These periods of high sympathetic activity during desynchronized sleep were often but not always related to rapid eye movements (fig. 6). The increase of total MSA was inversely correlated with the duration of the desynchronized (REM) sleep (fig. 7). This may be related to the finding that the longer the period of desynchronized sleep the shorter the relative duration of rapid eye

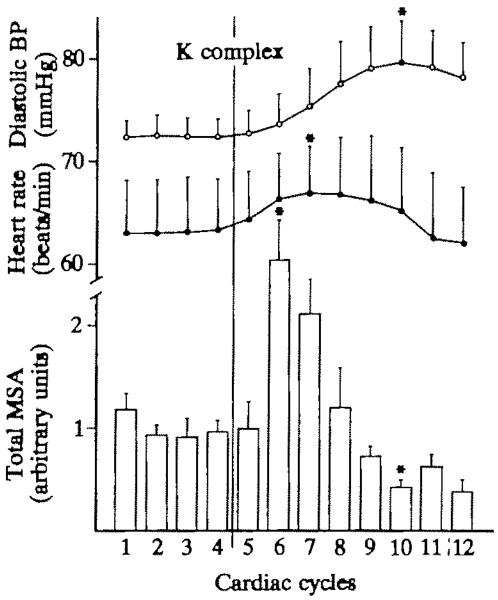

FIG 5. Changes of total muscle sympathetic activity (MSA), heart rate and diastolic blood pressure (BP) during 4 cardiac cycles preceding and during 8 cardiac cycles following the first sharp-wave peak of the K complexes (indicated by broken line) in 6 subjects. MSA values are normalized for the mean of the values obtained in 4 heart cycles preceding a K complex * Significant difference from the control level (the cardiac cycle immediately preceding the K complex).

movements. For example, in subject B.O. rapid eye movements comprised 22% of a 2 min period of desynchronized sleep and MSA increased to 170% of the awake value. In contrast, in subject N.E. rapid eye movements occurred during 8% of the 13.5 min period of desynchronized sleep and MSA increased to only 104% of the awake value.

DISCUSSION

We have measured sympathetic nerve activity in humans during sleep. Our main findings were: (1) muscle sympathetic nerve activity decreased during synchronized (non-REM) sleep; (2) in stage 2 there were transient increases of MSA and heart rate which were closely related to the occurrence of K complexes in the EEG recordings; (3) MSA increased during desynchronized (REM) sleep. The increase occurred mainly in short periods of high activity and was usually associated with rapid eye movements.

Decrease of MSA during synchronized (non-REM) sleep

Our finding of a decrease of MSA during non-REM sleep in humans agrees with data obtained in animal experiments. Direct recordings of sympathetic activity during synchronized sleep have been made in the renal nerve of the cat in which a decrease was observed (Baust *et al.*, 1968) but there is also evidence of vasodilatation in muscle, renal and mesenteric vascular beds in the cat (Mancia *et al.*, 1971).

The reduction of sympathetic outflow may be due to a reduced central sympathetic

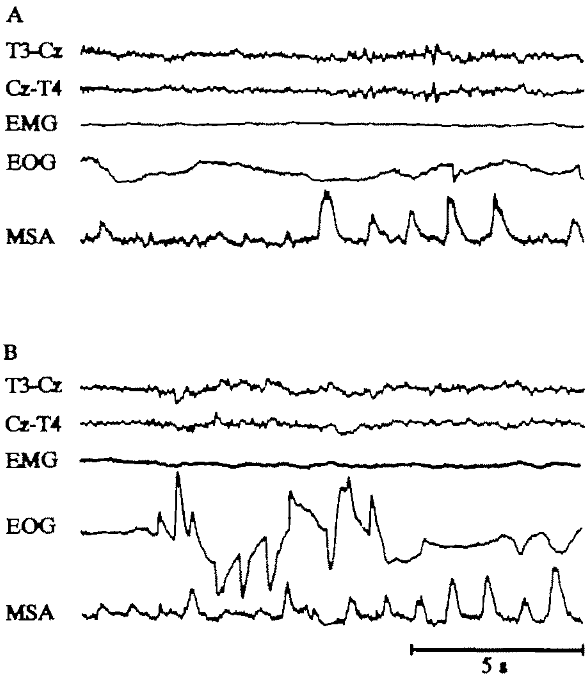

FIG. 6. Polygraphic recordings in 2 subjects (A, B). Short-lasting increases of MSA in desynchronized (REM) sleep may not (A) but usually are (B) associated with rapid eye movements. Abbreviations as in fig 1.

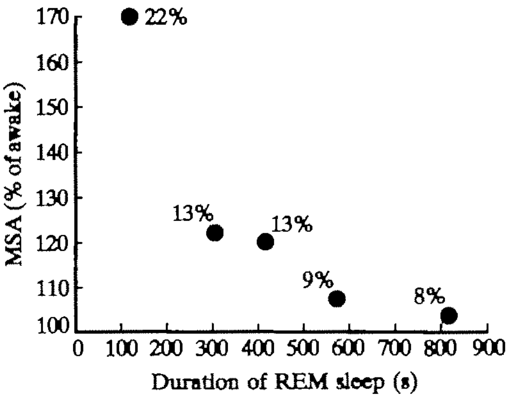

FIG. 7. Increase of total muscle sympathetic activity (MSA) during desynchronized (REM) sleep is inversely related to the duration of this sleep stage. Numbers above the dots indicate the relative duration of rapid eye movement periods during the whole desynchronized sleep

excitability. Experimental evidence of reduced neuronal activity in the brainstem and in other regions of the brain during non-REM sleep (Siegel, 1990) supports this assumption. In man, there are several studies showing that the baroreceptor-cardiac reflex is reset to lower blood pressure values during synchronized sleep (Bristow *et al.*, 1969; Smyth *et al.*, 1969; Conway *et al.*, 1983; Kasting *et al.*, 1987), whereas data about changes of the sensitivity of the reflex are inconsistent. No circadian variation of the sensitivity of the baroreceptor-heart rate reflex was found when subjects were investigated in the awake state or after awakening during normal sleep-waking cycles (Kasting *et al.*, 1987). However, Smyth *et al.* (1969) described an increased sensitivity during sleep which was similar in different sleep stages although, in a later study from the same group (Bristow *et al.*, 1969), no consistent change of sensitivity was found.

K complex-related increase of sympathetic activity

We found transient increases of MSA in stage 2 sleep which were related to spontaneous K complexes. What is the mechanism underlying this finding? An arterial baroreflex effect on MSA can probably be excluded since the increase of nerve traffic was not preceded by a decrease of blood pressure. The increase of blood pressure occurring about 4 s after the increase of MSA is in agreement with the result of a previous study (Wallin and Nerhed, 1982) on the time relationship between a transient increase of MSA and the succeeding blood pressure increase. Thus our interpretation is that a K complex is associated with a nonbaroreflex-mediated increase of vasoconstrictor drive to skeletal muscle vessels which contributes to a succeeding blood pressure increase. In contrast, the MSA reduction following the primary increase coincided with the blood pressure peak (fig. 5) and therefore probably was a baroreflex response.

The increase of MSA occurred approximately 1 s after the first sharp-wave peak of a K complex (fig. 5). Since there is a conduction delay for MSA from the brain to the peroneal nerve at the knee of slightly more than 1 s (Fagius and Wallin, 1980), it must be postulated that activation of sympathetic centres occurs at the same time as cortical activation, that is, in terms of time relationships both phenomena may have the same origin.

K complexes are often associated with slight movements, cessation of snoring or a sudden change of regular respiration. They may occur spontaneously or may be elicited by external stimuli and are considered as signs of abortive arousal (*see*, e.g., Roth *et al.*, 1956; Johnson and Karpan, 1968). This interpretation is supported by the finding that K complexes are often associated with signs of cutaneous vasoconstriction and sweating (Johnson and Karpan, 1968). Could the increase of MSA also be an arousal-related phenomenon? As mentioned in the Introduction, arousal stimuli do not influence MSA in awake healthy subjects. This may be due to an inhibitory influence of the baroreceptors on MSA: after temporary baroreceptor deafferentation (Fagius *et al.*, 1985) or cervical spinal cord lesions (Stjernberg *et al.*, 1986) interrupting baroreflex pathways, arousal responses in MSA do occur. Thus if baroreceptor influence on MSA were weakened, the K complex-related increases of MSA may also be arousal phenomena. Possibly the K complex is associated with a generalized sympathetic activation: besides the activation of skin sympathetic fibres causing cutaneous vasoconstriction and sweating, direct recordings in the cat showed an increase of renal sympathetic activity following arousal during synchronized sleep.

Whether there are transient K complex-related changes of baroreceptor reflex mechanisms has not been investigated systematically. However, Smyth *et al.* (1969) showed a figure in which the reflex bradycardia in response to a blood pressure increase was suddenly interrupted when a K complex occurred and, though the pressure continued to rise, the heart rate accelerated. This observation may be an example showing that the inhibitory influence of baroreceptors in stage 2 sleep cannot override a strong central sympathetic activation.

The functional importance of a K complex is unknown. However, if the K complex-related increase of sympathetic activity is an indicator of an (internally evoked?) generalized arousal, it may be speculated that it has survival value. During deep sleep the low responsiveness to external stimuli makes the individual vulnerable to external threats. Perhaps, therefore, stage 2 sleep is a preparation for deep sleep during which the K complex-related partial awakenings allow the individual a long enough appraisal of the 'danger situation' before and between periods of deep sleep.

In the rat, parallel changes in activity of the splanchnic sympathetic nerve and of noradrenergic neurons of the nucleus locus coeruleus have been demonstrated in several physiological situations (Elam *et al.*, 1981, 1984, 1986). The locus coeruleus has a key function for alerting reactions and has a widespread terminal network innervating the entire cortex (*cf* Foote *et al.*, 1983). Hypothetically, the simultaneous cortical K complexes and peripheral MSA increases could be a correlate in humans to the concomitant activation of peripheral and central noradrenergic neurons seen in rats.

Increase of MSA during desynchronized (REM) sleep

We found a clear increase of MSA in desynchronized sleep. A similar increase of muscle nerve sympathetic activity has been found also in decerebrate cats exhibiting desynchronized sleep-like periods. During such periods sympathetic traffic to the muscle vascular bed increased but traffic in renal, splanchnic, cardiac and lumbar sympathetic nerves decreased (Coote and Futuro Neto, 1981). In addition, the tonically reduced (background) level of activity was interrupted by sudden, short-lasting increases of sympathetic activity in all nerves (Coote, 1982).

In man, previous studies of desynchronized sleep showed a marked variability of mean blood pressure values (Snyder *et al.*, 1964; Coccagna *et al.*, 1971). It seems likely, from our findings, that short periods of strong activation of MSA contribute to this variability. The fact that no or only minor increases of blood pressure have been reported during desynchronized sleep (e.g., Snyder *et al.*, 1964; Khatri and Freis, 1967; Bristow *et al.*, 1969; Coccagna *et al.*, 1971) despite the increase of MSA may indicate that in humans as well, there is a decrease of sympathetic activity to other vascular beds similar to that demonstrated in animal experiments (*see above*). This would also agree with reports of decreased total peripheral resistance during desynchronized sleep in man (Khatri and Freis, 1967; Bristow *et al.*, 1969).

The mechanism behind the increase of sympathetic outflow to muscles during desynchronized sleep is not clear. Increased sensitivity of the baroreceptor-heart rate reflex has been reported in humans (Bristow *et al.*, 1969; Smyth *et al.*, 1969), but in a recent study in the cat the sensitivity of the reflex was found to be decreased during desynchronized sleep (Knuepfer *et al.*, 1986). Similar, perhaps only transient, suppressions of the reflex in humans cannot be excluded since another sympathetic reflex, the thermoregulatory reflex, is suppressed during desynchronized sleep in man (Obál, 1984). Another mechanism was suggested by Baccelli *et al.* (1974). They hypothesized on the existence of a spinal vascular reflex originating from the muscles themselves which would act during desynchronized sleep and would be suppressed in the awake state and during synchronized sleep.

Limitations of the study

We think that the findings in our study represent changes which occur in sleep during normal sleep-awake cycles. There are, however, two points which merit discussion. The study was made in partly sleep-deprived subjects and it is known that an acute reversal of the awake-sleep periods may alter the duration and frequency of sleep cycles (Weitzman *et al.*, 1970). Although we are not aware of any data on this point, we cannot exclude that sleep-related changes of sympathetic activity are also influenced by sleep deprivation. The existence of circadian rhythms of blood pressure (e.g., Richardson *et al.*, 1964; Snyder *et al.*, 1964)—perhaps related to circadian changes of the secretion of various hormones (e.g., corticoids, aldosterone, renin; for references, *see* Carandente, 1989)—would also affect our results. However, in a more recent study, Littler (1979) found no difference in blood pressure decrease during nocturnal and during daytime sleep. Based on his findings and on the re-evaluation of data published previously, he suggested that changes of arterial blood pressure are not specifically related to time but governed by physical activity and the state of sleep itself.

In summary, we recorded MSA in the peroneal nerve, in some experiments also blood pressure, during sleep in healthy subjects. During non-REM sleep the mean level of total MSA decreased. The decrease became apparent in stage 2 and continued in stage 3–4. In stage 2, we found transient increases of MSA which were associated with the occurrence of K complexes in the EEG. We suggest that K complex-related increases of MSA are signs of arousal and if so they may indicate a weakened inhibitory influence of baroreceptors on MSA. During desynchronized sleep MSA increased in short periods of high activity usually related to rapid eye movements.

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REFERENCES

Baccelli G, Albertini R, Mancia G, Zanchetti A (1974) Central and reflex regulation of sympathetic vasoconstrictor activity to limb muscles during desynchronized sleep in the cat. *Circulation Research*, **35**, 625–635.

Baust W, Weidinger H, Kirchner F (1968) Sympathetic activity during natural sleep and arousal. *Archives Italiennes de Biologie*, **106**, 379–390.

Bristow JD, Honour AJ, Pickering TG, Sleight P (1969) Cardiovascular and respiratory changes during sleep in normal and hypertensive subjects. *Cardiovascular Research*, **3**, 476–485.

Carandente O (1989) Hormones and blood pressure: clues from chronobiology. *Chronobiologia*, **16**, 45–88.

Cejnar M, Hunyor SN, Liggins GW, Davis RJ (1988) Description of a new continuous non-invasive blood pressure monitoring instrument. *Proceedings of the Australian Physiological and Pharmacological Society*, **19**, 90*P*.

Coccagna G, Mantovani M, Brignani F, Manzini A, Lugaresi E (1971) Arterial pressure changes during spontaneous sleep in man. *Electroencephalography and Clinical Neurophysiology*, **31**, 277–281.

Conway J, Boon N, Jones JV, Sleight P (1983) Involvement of the baroreceptor reflexes in the changes in blood pressure with sleep and mental arousal. *Hypertension*, **5**, 746–748.

Coote JH (1982) Respiratory and circulatory control during sleep. *Journal of Experimental Biology*, **100**, 223–244.

Coote JH, Futuro Neto HA (1981) Pattern of sympathetic activity to different vascular beds during paradoxical sleep. *Journal of Physiology, London*, **312**, 29*P*–30*P*.

Delius W, Hagbarth K-E, Hongell A, Wallin BG (1972) General characteristics of sympathetic activity in human muscle nerves. *Acta Physiologica Scandinavica*, **84**, 65–81.

Elam M, Yao T, Thorén P, Svensson TH (1981) Hypercapnia and hypoxia: chemoreceptor-mediated control of locus coeruleus neurons and splanchnic, sympathetic nerves. *Brain Research, Amsterdam*, **222**, 373–381.

Elam M, Yao T, Svensson TH, Thorén P (1984) Regulation of locus coeruleus neurons and splanchnic, sympathetic nerves by cardiovascular afferents. *Brain Research, Amsterdam*, **290**, 281–287.

Elam M, Svensson TH, Thorén P (1986) Locus coeruleus neurons and sympathetic nerves: activation by cutaneous sensory afferents. *Brain Research, Amsterdam*, **366**, 254–261.

Fagius J, Wallin BG (1980) Sympathetic reflex latencies and conduction velocities in normal man. *Journal of the Neurological Sciences*, **47**, 433–448.

Fagius J, Wallin BG, Sundlöf G, Nerhed C, Englesson S (1985) Sympathetic outflow in man after anaesthesia of the glossopharyngeal and vagus nerves. *Brain*, **108**, 423–438.

Foote SL, Bloom FE, Aston-Jones G (1983) Nucleus locus ceruleus: new evidence of anatomical and physiological specificity. *Physiological Reviews*, **63**, 844–914.

Gassel MM, Ghelarducci B, Marchiafava PL, Pompeiano O (1964) Phasic changes in blood pressure and heart rate during the rapid eye movement episodes of desynchronized sleep in unrestrained cats. *Archives Italiennes de Biologie*, **102**, 530–544.

Guazzi M, Zanchetti A (1965) Blood pressure and heart rate during natural sleep of the cat and their regulation by carotid sinus and aortic reflexes. *Archives Italiennes de Biologie*, **103**, 789–817.

Johnson LC, Karpan WE (1968) Autonomic correlates of the spontaneous K-complex. *Psychophysiology*, **4**, 444–452.

Kasting GA, Eckberg DL, Fritsch JM, Birkett CL (1987) Continuous resetting of the human carotid baroreceptor-cardiac reflex. *American Journal of Physiology*, **252**, R732–R736.

Khatri IM, Freis ED (1967) Hemodynamic changes during sleep. *Journal of Applied Physiology*, **22**, 867–873.

Knuepfer MM, Stumpf H, Stock G (1986) Baroreceptor sensitivity during desynchronized sleep. *Experimental Neurology*, **92**, 323–334.

Littler WA (1979) Sleep and blood pressure: further observations. *American Heart Journal*, **97**, 35–37.

Mancia G, Baccelli G, Adams DB, Zanchetti A (1971) Vasomotor regulation during sleep in the cat. *American Journal of Physiology*, **220**, 1086–1093.

Mancia G, Zanchetti A (1980) Cardiovascular regulation during sleep. In: *Physiology in Sleep*. Edited by J. Orem and C. D. Barnes. New York and London: Academic Press, pp. 1–55.

Matousek M, Petersén I (1983) A method for assessing alertness fluctuations from EEG spectra. *Electroencephalography and Clinical Neurophysiology*, **55**, 108–113.

Obál F (1984) Thermoregulation and sleep. *Experimental Brain Research*, Supplement 8, 157–172.

Rechtschaffen A, Kales A (1968) *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*. Washington, DC: Public Health Service, US Government Printing Office.

Richardson DW, Honour AJ, Fenton GW, Stott FH, Pickering GW (1964) Variation in arterial pressure throughout the day and night. *Clinical Science*, **26**, 445–460.

Roth M, Shaw J, Green J (1956) The form, voltage distribution and physiological significance of the K-complex. *Electroencephalography and Clinical Neurophysiology*, **8**, 385–402.

Siegel JM (1990) Mechanisms of sleep control. *Journal of Clinical Neurophysiology*, **7**, 49–65.

Smyth HS, Sleight P, Pickering GW (1969) Reflex regulation of arterial pressure during sleep in man: a quantitative method of assessing baroreflex sensitivity. *Circulation Research*, **24**, 109–121.

Snyder F, Hobson JA, Morrison DF, Goldfrank F (1964) Changes in respiration, heart rate, and systolic blood pressure in human sleep. *Journal of Applied Physiology*, **19**, 417–422.

Stjernberg L, Blumberg H, Wallin BG (1986) Sympathetic activity in man after spinal cord injury: outflow to muscle below the lesion. *Brain*, **109**, 695–715.

Sundlöf G, Wallin BG (1977) The variability of muscle nerve sympathetic activity in resting recumbent man. *Journal of Physiology, London*, **272**, 383–397.

Wallin BG, Nerhed C (1982) Relationship between spontaneous variations of muscle sympathetic activity and succeeding changes of blood pressure in man. *Journal of the Autonomic Nervous System*, **6**, 293–302.

Wallin BG, Fagius J (1988) Peripheral sympathetic neural activity in conscious humans. *Annual Review of Physiology*, **50**, 565–576.

Weitzman ED, Kripke DF, Goldmacher D, McGregor P, Nogeire C (1970) Acute reversal of the sleep-waking cycle in man: effect on sleep stage patterns. *Archives of Neurology, Chicago*, **22**, 483–489.

Yamakoshi K, Rolfe P, Murphy C (1988) Current developments in non-invasive measurement of arterial blood pressure. *Journal of Biomedical Engineering*, **10**, 130–137.

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AMNESIA FOLLOWING DAMAGE TO THE LEFT FORNIX AND TO OTHER SITES

A COMPARATIVE STUDY

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SUMMARY

Two memory-impaired patients, who had suffered damage to the left or both fornix columns during removal of a ventricular cyst, were compared with 3 others having left-sided hippocampal or thalamic lesions, and with normal controls. The tests used were nonverbal—scene recognition, delayed matching-to-sample and concurrent pattern and object discrimination learning. The last two are differentially sensitive to fornix transection and to hippocampal or thalamic ablations in monkeys; however, the patients with fornix damage did not show a distinctive pattern of impairment. The reasons for this discrepancy are discussed. The study adds to the evidence that fornix transection can cause wide-ranging memory disturbances in man.

INTRODUCTION

The fornix interconnects the hippocampus and the mamillary nuclei; one or other of those structures is commonly damaged in patients with the amnesic syndrome (Brierley, 1977; Mair *et al.*, 1979). However, there is a persisting controversy as to whether transection of the fornix has any effect on memory in man (for reviews, *see* Parkin, 1984; Garcia-Bengochea and Friedman, 1987). Much of the evidence that there is such an effect has derived from patients who develop memory impairment following removal of a colloid cyst from the third ventricle, an occasional but well-known side-effect of such surgery (Cairns and Mosberg, 1951; Poppen *et al.*, 1953; Nitta and Symon, 1985). The most plausible cause is damage to the anterior columns of the fornix, which run close to the foramen of Monro and may either be deliberately sectioned or accidentally damaged in the course of gaining access to the cyst through the foramen (Carmel, 1985). Memory impairments have been reported after ostensibly unilateral (Cameron and Archibald, 1981; Carmel, 1985) as well as bilateral (Sweet *et al.*, 1959; Christiansen, 1970; Jeeves *et al.*, 1979) fornix section; usually, of course, the true extent of fornix damage is unknown.

In this paper we report a study of 2 patients who developed disabling memory problems following transcallosal removal of a colloid cyst via the left lateral ventricle. Unintended damage to the fornix, principally on the left, had been caused in both cases. We examined the pattern of impairment they showed on a series of visual memory tasks modelled

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on those used to study the effects of lesions on the fornix and other structures on memory in monkeys. The performance of the 2 colloid cyst (fornix) patients was compared with that of 3 patients who became amnesic following cerebrovascular lesions which affected other sites—the hippocampus or thalamus—but again predominantly on the left side. Normal control subjects were also tested.

The tasks were concurrent learning of several pattern and object discriminations, and recognition memory for pictures of complex scenes. A test of delayed matching-to-sample with abstract patterns was also included.

Bilateral fornix transection does not affect the ability of monkeys to learn several object discriminations concurrently (Moss *et al.*, 1981; Zola-Morgan *et al.*, 1989) or to perform an analogous task where lists of objects are presented and the monkey must recall which were associated with food and which not (Gaffan *et al.*, 1984*b*). However, both hippocampal ablation (Moss *et al.*, 1981; Mahut *et al.*, 1982; Zola-Morgan *et al.*, 1989) and dorsal thalamic lesions (C. Lim and D. Gaffan, unpublished) have been reported to impair concurrent object discrimination learning. On this basis we might expect the fornix cases to have relatively little difficulty with concurrent discrimination learning, compared with the other patients. However, fornix transection does disrupt the ability of monkeys to recognize complex pictures (Gaffan, 1977) and the relative position of elements within a scene (Gaffan and Saunders, 1985; Gaffan and Harrison, 1989). Accordingly we expected the fornix cases to be no less impaired than the other amnesics at scene recognition.

In the case of delayed matching-to-sample, fornix transection, hippocampal ablation and dorsal thalamic lesions have been variously reported either to impair performance at this task or not, depending on the degree of difficulty (in terms of retention interval or length of the list of items to be remembered) and other procedural details (*see* Gaffan, 1974; Owen and Butler, 1981; Mishkin, 1982; Gaffan *et al.*, 1984*a, c*; Bachevalier *et al.*, 1985; Zola-Morgan and Squire, 1985; Aggleton, 1986; Zola-Morgan *et al.*, 1989). The version we used, requiring subjects to match from lists of 3 abstract patterns, was not one for which strong predictions about lesion effects could be made. We used the task in an exploratory manner, and also to occupy subjects during a retention interval with another procedure.

All the tasks, consonant with their original purpose of testing memory in animals, could be described as tests of visual or nonverbal memory. It was therefore conceivable, at the outset, that none of our amnesic subjects would be much impaired at any of them, because as expected from the predominantly left-sided lesions (*see* Milner, 1972), their deficits on standard tests were most apparent in verbal memory. In the event we did observe clear amnesic impairments in some of the tests. That fact raises questions about the nature of the performance of humans and animals in operationally similar tasks, which we discuss below.

SUBJECTS

The 5 amnesic patients, 2 who had undergone surgery to remove colloid cysts and 3 who had suffered cerebrovascular lesions, were all right-handed and their brain damage was known or suspected to be predominantly left-sided. In all cases the memory problem was the only cognitive disturbance and was severe enough to disrupt their daily life and work. None was profoundly amnesic; as might be expected, in most cases the anterograde deficit was largely confined to verbal material. The individual cases are described below in 2 subgroups according to aetiology. A group of 12 normal controls was also tested.

Colloid cyst (fornix) cases (Cases 1 and 2)

Since these 2 patients underwent the same surgical procedure and the preoperative and postoperative course of their symptoms was in many respects similar, they are described jointly where appropriate. Fuller details are given by Hodges and Carpenter (1991).

Case 1 (W.R.), a female clerk aged 45 yrs, was referred with a 12 month history of severe intermittent headaches with sporadic numbness and weakness of the left leg. *Case 2* (G.Y.), a 34-yr-old male salesman, had a 3 month history of paroxysmal headaches and loss of consciousness. Both were working regularly, and no problems with memory or other cognitive function were apparent from informal report or bedside testing.

Cranial CT scans in both showed a typical high-density nonenhancing cyst 1–2 cm in diameter lying in the midline within the third ventricle. Case 2 showed minimal enlargement of the lateral ventricles; Case 1 had a mild degree of obstructive hydrocephalus. Both underwent the same surgical procedure. A 2 cm incision was made in the corpus callosum, sparing the pericallosal arteries. The left lateral ventricle was entered, a hole made in the septum pellucidum, and the septal veins were coagulated. The colloid cyst had in each case been embedded in the septum pellucidum and was removed via the left foramen of Monro, without immediate apparent damage to the fornices. A drainage tube was left in place.

Postoperatively it soon became evident that both patients had developed an amnesic syndrome with severe anterograde impairment but relative sparing of retrograde memory. Initially the anterograde deficit was severe for both verbal and nonverbal material, but when formal testing was repeated at intervals over 6–12 months after the operation, there was substantial recovery of nonverbal but not of verbal memory. Both patients had to discontinue work because of their persisting memory difficulties. At the time of the present study, 3 yrs postoperatively for Case 1 and 1 yr for Case 2, both, however, had returned to work with their former employers but in a sheltered capacity. For example, Case 2 now works as a clerk rather than as a salesman. While still suffering memory problems, they both have insight into these symptoms. Case 2 in particular makes spontaneous use of visual imagery techniques to aid his work.

With the surgical approach that was employed, unintended damage to one or both anterior columns of the fornix is the most plausible cause of the memory impairment. The site of operation was well forward of the posterior thalamus. CT scans were obtained postoperatively; in both cases an area of low attenuation was evident in the region of the left anterior column of the fornix (*see* fig. 1). MRI scans, performed around the time of the present study, confirmed that the fornix was largely destroyed anterior to the operation site. In Case 2, the right fornix was partly preserved, while in Case 1 both fornix columns appeared to be damaged (*see* fig. 2). In these midline sections, the mamillary nuclei cannot be positively identified in either patient. All other memory-related structures (i.e., thalamic nuclei, mamillothalamic tract, hippocampus, amygdala and parahippocampal region) appeared normal. There must, then, be a strong presumption that direct or indirect (e.g., vascular) damage to the fornix was responsible for the amnesia in both patients.

Patients with cerebrovascular lesions (Cases 3–5)

Case 3 (V.C.), a female cook, presented at age 59 yrs with the sudden onset of drowsiness and general confusion, which resolved over the next 2 wks. At this time a CT scan (fig. 3) showed a thalamic haemorrhage involving predominantly the left dorsomedial area. The only long-lasting consequence has been anterograde and retrograde amnesia. She was unable to return to work; she continues most household activities but relies on her husband for help with schedules, shopping lists, etc.

Case 4 (W.J.), a retired male chemical engineer aged 69 yrs, experienced a sudden loss of recent memory accompanied by abnormal skin sensation on the right side. A CT scan showed an area of ill-defined infarction of the left thalamus, involving the dorsomedial and lateral nuclei (fig. 4). No other cognitive impairment was noted and his anterograde memory deficit is confined to verbal material.

Case 5 (D.C.), a female domestic worker, suffered 2 episodes of cerebral infarction at age 40 and 42 yrs. The first involved the right middle cerebral artery. Her left hemiplegia resolved completely and she remained physically well without cognitive deficits until the second stroke which affected the left posterior cerebral artery. She presented with acute memory loss and a right upper quadrantic field defect. A CT scan showed infarcts in the territory of both arteries; that on the left involved the hippocampus and

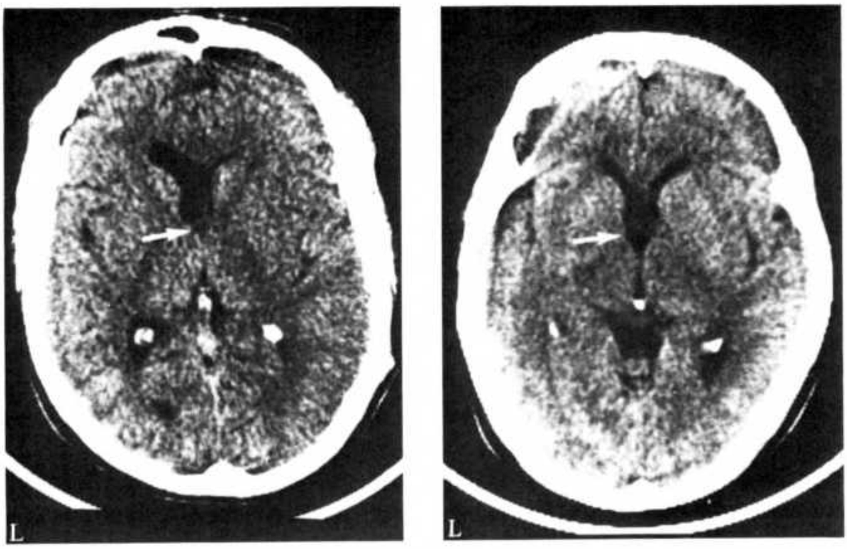

FIG. 1. CT scans at the level of the foramen of Monro; *Cases 1* (*left*) *and 2* (*right*). In both there is an area of low attenuation in the region of the left fornix (arrows). In Case 1, the left lateral ventricle is dilated (right decompressed by ventriculoperitoneal shunt, not shown).

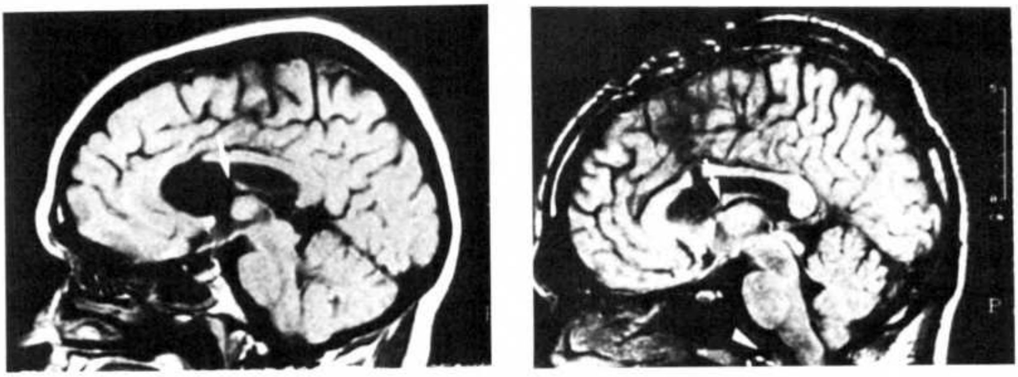

FIG. 2. Sagittal MRI images through the midline; *Case 1* (*left*) and *Case 2* (*right*). In both, the fornix is interrupted (arrows) at the level of the foramen of Monro, directly below the surgical corpus callosum deficit, which was more extensive in Case 1. In Case 2, the right fornix column was apparent on contiguous parasagittal cuts, but in Case 1 neither column could be demonstrated.

parahippocampal gyrus (fig. 5). Her amnesic syndrome has remained stable. At the time of testing she had not returned to work (although she has since been able to resume) and her social life was curtailed. Full investigation including 4-vessel cerebral angiography, echocardiography and coagulation screens has failed to reveal a cause for the strokes.

The results of formal testing of verbal and nonverbal memory and of retrograde amnesia with all 5 patients are summarized in Table 1. All show severe deficits of long-term verbal memory as reflected in the delayed tests of paragraph recall and paired-associate learning. The impairments in the nonverbal tests such as the Rey figure recall and Corsi block supraspan learning are more variable; Cases 1, 2 and 4 achieve normal scores on those tests, and although Cases 3 and 5 show some impairment it is clearly less marked than in the case of the verbal tests. This pattern is as expected given the predominantly left-sided lesions.

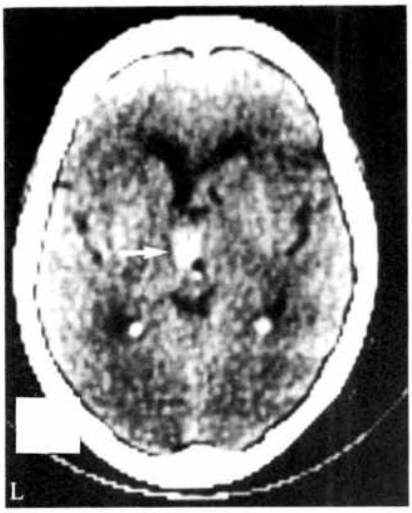

FIG. 3. *Case 3*. CT scan showing a haemorrhage in the left thalamus (arrow) displacing the third ventricle to the right.

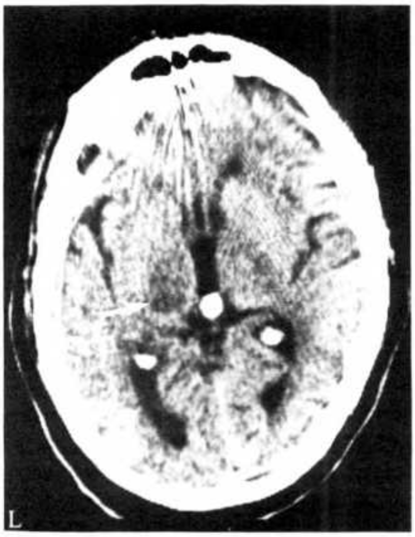

FIG. 4. *Case 4*. CT scan at the level of the pineal showing a large low density area in the left thalamus.

The extent of retrograde amnesia is a composite estimate based on several tests of memory for public events, personalities and autobiographical episodes (Hodges and Ward, 1989).

Control subjects

The control group was composed of 12 normal volunteers, 9 female and 3 male, who were paid for participating. Their age range (35 – 72, mean 54.7, yrs) was similar to that of the amnesic group as a whole (35 – 71, mean 52.4, yrs). Occupations and educational levels were as diverse as those of the amnesic subjects. The mean full-scale IQ for the controls as estimated from the National Adult Reading Test (NART; Nelson, 1982) was 109.7 (range 95 – 123). The corresponding mean across the 5 amnesics was 104.6 (range 95 – 120), while their mean WAIS full-scale IQ was 109.8. Neither the age nor the IQ scores of the control group differed significantly from those of the amnesic group as a whole (ts < 1).

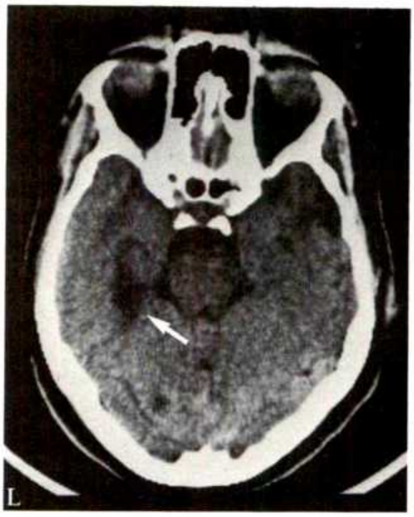

FIG. 5. *Case 5*. CT scan through the temporal lobes at the level of the cerebral peduncles showing an area of low density in the left hippocampus and parahippocampal gyrus (arrow).

METHODS

The experimental tests were administered individually to each subject in a single session lasting 2.5 – 3 h including rests; the only exception was Case 1 who carried out the first 3 tasks during a single session, and the second 3 tasks in a second session 5 wks later. The apparatus employed for each task is described below. The order of testing was the same for each person, as follows.

1. *Picture acquisition (scenes)*. Fifty colour slides were projected on a screen, about 2 m from the subject, for 7.5 s each with 1.5 s intervals. All slides showed landscapes, town views or large buildings. Human figures appeared in some but, if so, occupied only a small portion of the picture. The slides were shown twice through in the same order. At the first presentation of each slide, the subject was asked to say whether the place shown appealed to him/her or not, and on the second time, to judge whether the place was in Britain or abroad. The 2 presentations occupied about 10 min in all.

2. *Concurrent pattern discrimination with visual feedback*. This was closely similar (the exceptions being noted below) to an experiment with Korsakoff amnesics by Gaffan *et al*. (1990) who have provided a fuller description of the apparatus and the range of stimuli. The stimuli and procedure were modelled on those employed by Gaffan *et al*. (1989) in studies of the effects of medial temporal lesions upon pattern discrimination learning by monkeys.

The task consisted of a series of trials separated by 5 s intervals. During a trial a pair of coloured patterns was displayed side-by-side on a computer-controlled monitor screen which was touch-sensitive. Each pattern was composed of 2 superimposed symbols (e.g., rotated Greek characters) differing in colour. In each pair one pattern, if touched, flashed on and off followed by a bleep sound. Touching the other pattern simply made both patterns disappear. Subjects were asked to learn which patterns flashed and to touch those every time they appeared.

Three sets of pairs were employed, comprising 2, 6 and 10 pairs, respectively. The pairs within each set had to be learned concurrently, that is, intermingled. All pairs from the set appeared once in random sequence (Run 1) then again in a different random sequence (Run 2) and so on. During the first run through each set, it was prearranged that the subject's choices should be correct (cause the pattern to flash) with half the pairs, incorrect with the rest. Thereafter the identity of the correct and incorrect pattern within each pair was arranged to be consistent with the results of that subject's choices during the first run. This procedure reduces variability by ensuring all subjects start from the same level, 50% correct, regardless of initial preferences for particular patterns.

Problem 1 (2 pairs) continued until the subject completed 3 successive runs without errors, or for

TABLE 1. DETAILS AND NEUROPSYCHOLOGICAL TEST RESULTS OF AMNESIC PATIENTS

	Case 1 (F)	*Case 2 (M)*	*Case 3 (F)*	*Case 4 (M)*	*Case 5 (F)*
Diagnosis	*Colloid cyst (L fornix)*		*L thal. haem*	*L thal. infct*	*L medial temp. infct*
Age at onset (yrs)	45	34	59	69	42
Time of testing (mos postonset)	25	6	30	4	2
WAIS IQ					
Verbal	97	112	93	124	107
Performance	120	114	113	123	101
Full scale	107	110	102	125	105
NART—premorbid IQ	103	110	95	120	109
Digit span					
Forwards	6	9	7	8	8
Backwards	5	5	4	6	7
Verbal recall (Wechsler)					
Paragraph					
Immediate	3.5	8	3	3.5	5
Delayed (40 min)	0	0	0	0	0
Paired associates					
Immediate	8	4	6	7	11.5
Delayed (40 min)	5	0	2	4	6
Warrington recognition test					
Words	43	42	29	35	36
Faces	45	41	35	43	43
Nonverbal memory					
Rey figure					
Copy	34	33	31	31	26
Recall (40 min)	19	20	6	15	8.5
Benton Visual Reproduction					
Correct	6	6	3	7	3
Errors	7	5	15	7	11
Retrograde amnesia					
Estimated extent (yrs)	<1	<1	20+	10+	10+

10 runs (20 trials) at most. In Problems 2 and 3 (6 and 10 pairs, respectively) the criterion was 3 successive runs with no more than 1 error in total (i.e., at least 17/18 or 29/30 correct). The maximum number of runs was 15, that is 90 trials for Problem 2 or 150 trials for Problem 3.

The main respects in which this procedure differed from that of Experiment 1 of Gaffan *et al* (1990) were that in the present case money rewards were not given for correct choices, the 3 concurrent problems were given within a single session, and the stimuli, though drawn from a similar population, were not identical.

3. *Picture recognition test.* 100 colour slides were presented, including the 50 shown previously, randomly intermingled with new slides of similar types of scenes. The subject had to say which were old (seen previously) and which new, and to guess if not sure. Each slide remained on screen until the subject responded. The retention interval between tasks 1 and 3 varied according to the duration of task 2. The average interval was 47 min and it was not significantly different between groups.

4. *Concurrent object discrimination.* This procedure is a close analogue of 'junk-object' discrimination as learned by monkeys in a Wisconsin General Test Apparatus. Similar tasks have been given to Korsakoff amnesics by Oscar-Berman and Zola-Morgan (1980), Aggleton *et al.* (1988) and Squire *et al.* (1988) using coins rather than marbles as rewards.

Sixteen pairs of 'junk' objects were chosen which did not have obvious common names (e.g., unusual bits of electrical equipment, odd-shaped pieces of plastic). Each pair was presented to the subject on a wooden board having two small dips (wells) 30 cm apart, each covered by an object. One object in each pair always had a marble under it and the subject's task was to learn which objects had marbles, displace these and collect the marbles. The object with the marble was equally often over the left and the right well. A screen hid the board from the subject's view while the objects and marbles were being positioned, and the experimenter simulated placing a marble in both holes to avoid giving auditory clues to its location. Trials were presented at intervals of 25–30 s.

The 16 pairs of objects were presented 3 times through in a fixed order. During the first run, there were in fact marbles under both objects on half the trials and under neither object on the remaining trials, so all subjects found a marble on 8/16 occasions. As in task 2, the assignment of marbles to objects in later runs was arranged to be consistent with the results of first-run choices. If a subject made 16 correct choices during Run 2 (only 1 person did), Run 2 was omitted.

5. *Delayed matching-to-sample, random patterns.* The same computer apparatus was used as for task 2. Stimuli were displayed on the touch-sensitive monitor screen. Each stimulus was made up of 2 superimposed, different coloured patterns as in task 2 but the patterns were 'random walk' traces made of 3–9 joined straight lines of random orientation and length (*see* Gaffan *et al.*, 1990, for examples). Each trial of the task comprised a series (list) of 3 'sample' patterns, presented successively, followed by 3 test presentations during which memory for those samples was assessed. Each sample was displayed singly at the centre of the computer screen. A sample remained until the subject touched it, whereupon the screen went blank for 2 s, then the next sample appeared. One second after the last sample disappeared, the first of the 3 tests was presented. At each test, 4 patterns, only 1 of which was identical to (matched) a preceding sample, were displayed equidistant from the centre. The position of the matching stimulus was randomly distributed among the 4 possibilities. The subject's task was to touch the matching stimulus; correct responses generated a beep as feedback. The interval between tests was about 3 s. Samples were tested in reverse order, that is, the first test included sample 3, the second, sample 2 and the third, sample 1. After the third test there was a blank interval of 12 s before the next list of 3 new samples commenced.

The task was given in 2 blocks of 16 trials, each block lasting 12–15 min. Between blocks the subjects rested and completed the NART reading test.

6. *Delayed retention test, objects.* The 16 object pairs from task 4 were presented for 1 more run as before. Subjects had not been warned they would be retested. The interval between tests 4 and 6 varied according to the duration of test 5 but was on average 46 min and did not differ between the groups.

Statistical analysis

Parametric statistical tests, e.g., Student's t for comparisons between the amnesic and control groups, are reported throughout. Occasionally, where distributions of data departed considerably from normality, nonparametric tests (e.g., Mann-Whitney U) were also applied. In all cases the conclusions were unaffected.

Since both amnesic and control groups varied widely in age and IQ, we made a preliminary check on the control data for possible relationships between age, IQ and performance on any of the memory tests. None of the test scores was significantly correlated with age or IQ. The one which had the largest correlation with age was total correct responses in the 6-pair concurrent discrimination (Pearson $p = -0.408$). IQ was most strongly related to performance on scene recognition and 10-pair concurrent learning ($P = 0.435$ and 0.532, respectively). Only the last value approached the criterion for significance (0.576 with 10 df).

RESULTS

Scene recognition (see Table 2)

The amnesic group made significantly more errors than the controls ($t = 3.11$, $df = 15$, $P < 0.01$). Thus, despite their relatively mild impairment in nonverbal memory according to the standard tests shown in Table 1, they clearly had some difficulty with this task. The correlation between scene recognition accuracy and IQ, noted in the control group, is also evident in the amnesic data ($p = 0.88$, df = 3, $P < 0.05$). The 2 fornix cases fell within the range of the other amnesics.

TABLE 2 TEST SCORES OF INDIVIDUAL AMNESIC SUBJECTS AND CONTROLS

	Fornix lesions		*Cerebrovascular lesions*			*Amnesics (mean)*	*Controls ($n = 12$) (mean)*
Case	1	2	3	4	5		
Sex	F	M	F	M	F		
Age (yrs)	49	35	64	71	43	52.4	54.7
IQ (estimated)	99	100	95	120	109	104.6	109.7
Scene recall errors/100	7	8	14	2	6	7*	1.5*
Concurrent patterns							
Total errors, Run 2 onwards							
2 pairs	7	8	2	0	1	2*	0*
6 pairs	23	19	37	11	26	23.2	15.8
%	27	23	44	13	31	27.6	18.8
10 pairs	68	28	41	35	34	41.2	20.0
%	48	20	29	25	24	29.4	14.3
Concurrent objects							
Total errors, Runs 2–4	18	10	10	6	13	11.4	5.2
%	37	21	21	12	27	21.2	10.9
Matching-to-sample, % errors	40	10	62	15	26	30.6	16.2

* Median.

Concurrent pattern discrimination

The acquisition curves for each of the 3 concurrent sets are shown in fig. 6. Subjects who had reached criterion were assigned a score of 100% on later runs. Table 2 also summarizes the individual scores (total errors) for the amnesics on each problem.

The amnesics were impaired relative to the controls on each concurrent problem; statistically, their deficit was more severe on the first (2-pair) and the third (10-pair) problems than on the second (6 pairs). Comparing the total errors made during each problem, the amnesics were significantly worse than the controls on the 2-pair and the 10-pair problem ($t = 3.09$ and 3.44, respectively, df = 15, $P < 0.01$) but did not differ significantly on the 6-pair problem ($t = 1.57$). As Table 2 shows, 1 of the 2 fornix patients did far worse than the other, but again they fell within the range of the other amnesics.

Concurrent object discrimination

As fig. 7 shows, the amnesic group, particularly the fornix patients, were impaired throughout. They did not show exceptionally poor retention on the delayed test, however.

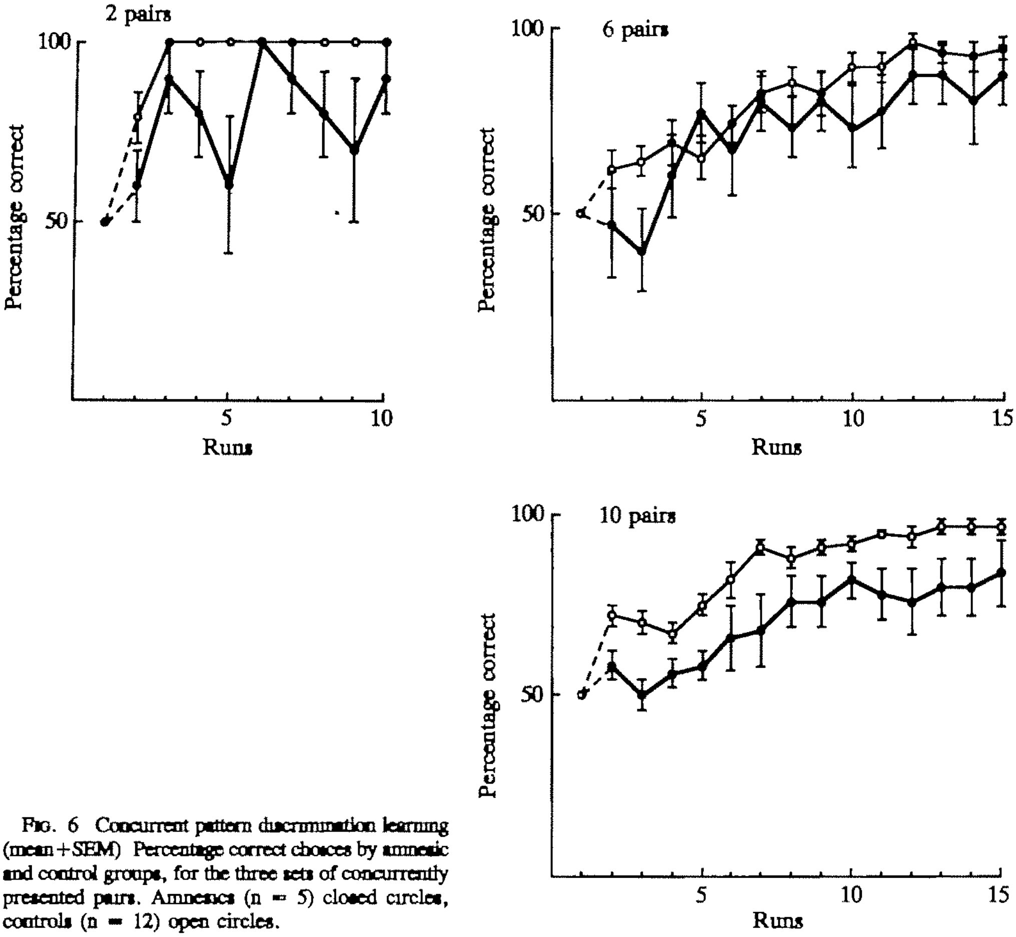

FIG. 6 Concurrent pattern discrimination learning (mean+SEM) Percentage correct choices by amnesic and control groups, for the three sets of concurrently presented pairs. Amnesics (n = 5) closed circles, controls (n = 12) open circles.

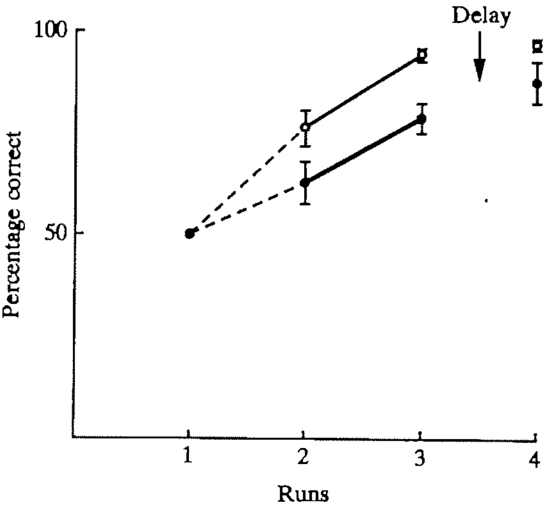

FIG. 7. Concurrent object discrimination learning (mean+SEM). Correct choices by amnesic and control groups while learning 16 pairs of objects concurrently The first 3 runs occurred in close succession, the fourth after approximately 40 min filled delay Symbols as in fig. 6.

The groups differed significantly on total errors across Runs 2, 3 and 4 (t = 2.95, df = 15, $P < 0.01$). Although direct comparison is impossible because the number of pairs and other procedural features differ, the deficit of our amnesic group in concurrent object discrimination seems less severe than that of the Korsakoff patients tested by Oscar-Berman and Zola-Morgan (1980) or Squire *et al.* (1988).

Delayed matching

Fig. 8 shows the recognition performance for the control group at each list position, chance level being 25% correct because each test offered 4 choices (*see also* Table 2). The individual scores for the amnesics are superimposed. One of them (Case 3) apparently failed to notice that the last pattern of each list was always tested immediately, but all the other amnesics, like the controls, did so and took advantage of this to score highly on that item. Statistically, while the amnesics performed worse overall than controls, the difference arose mainly from this last item. On the first 2 list positions combined, the group difference was not significant (t = 1.79). In view of the wide individual variation, this is hard to interpret. Once again the 2 fornix cases were not distinctive; 1 performed well, the other poorly.

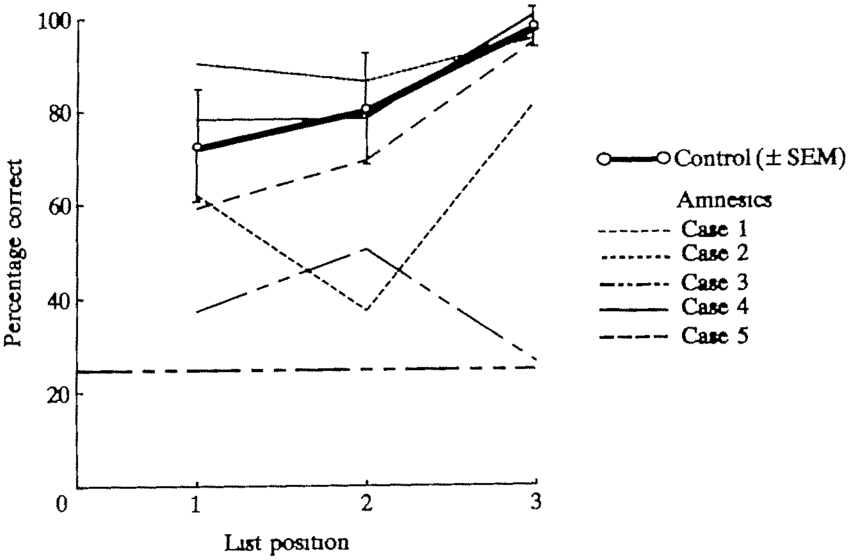

Fig. 8. Delayed matching-to-sample (mean+SEM). Correct choices by controls, and individual correct scores of 5 amnesic subjects. On each trial a list of 3 samples was presented and then tested in reverse order, i.e., list position 3 tested first. The horizontal line indicates chance performance (25% correct).

DISCUSSION

Our first aim was to compare the performance of the two aetiological subgroups of amnesics. Damage to the fornix in the absence of pathology in any other memory-related structures (Cases 1 and 2) produces a moderate but disabling amnesia which does not, on our tests, differ distinctively from that resulting from predominantly left-sided damage to the hippocampus or thalamus in our other subjects, Cases 3–5.

Impairment in Case 1 was generally slightly worse than in Case 2. She sustained more damage, not only to the fornix but also to the anterior corpus callosum. Clark and Geffen (1989) in a recent review, argued that there is no satisfactory evidence that callosal section per se affects memory. They concluded that impairments occur only when extracallosal structures, such as the fornix or hippocampal commissure, are additionally involved. A recent suggestion (Valenstein *et al.*, 1987) that retrosplenial cortex may subserve memory is not relevant to Case 1, as her lesion was more anterior. We consider that her deficit was greater than Case 2 because her fornix lesion was more complete, affecting both columns.

Case 2, together with Case 4 who had a thalamic lesion, were completely unimpaired at delayed matching-to-sample. That is unsurprising. The difficulty of the task was not severe, and it must be remembered that the primary deficit in these patients was in verbal memory; the matching-to-sample task, whose stimuli were designed to be hard to describe, was arguably the most purely 'nonverbal' of all. Moreover, Case 2 had taught himself to use visual mnemonic techniques. Indeed, the exceptional failure to find a consistent amnesic impairment in this task underlines the contrast with the other tasks. Although these were modelled on 'nonverbal' tests for animals, and we attempted to restrict the nameability of the stimuli in most cases, all the amnesics were clearly impaired at concurrent learning of pattern and object discrimination, and scene recognition. It would seem either that we are wrong to consider these tasks nonverbal, or that the patients could not easily deploy their relatively intact visual memory to cope with the tasks, or both.

Our second aim was to compare the performance of the amnesics with the reported effects of specific lesions on similar tasks in monkeys. Of course the patients' lesions were generally left-sided while the studies with monkeys employed bilateral lesions. It could be argued that, if patients show a different pattern of lesion effects than do monkeys, this might be because their lesions primarily disrupt verbal memory. However, as we have remarked, the amnesics were impaired on our tasks despite their operationally nonverbal character. Our discussion therefore assumes that qualitatively similar results would have been observed had the lesions been bilateral.

Considering scene recognition first, fornix transection disrupts the ability of monkeys to recall the appearance, or relative positions of features, in complex scenes (Gaffan, 1977; Gaffan and Saunders, 1985; Gaffan and Harrison, 1989) and this is more sensitive to fornix transection than is the recall of individual objects as in matching-to-sample (Gaffan *et al.*, 1984*a*). The effects of ablating the hippocampus or thalamic nuclei on scene memory have not been studied, but certainly hippocampectomy would be expected to have at least as severe an effect as fornix transection. Our results confirm that the fornix patients, and 2 of the other 3 amnesics, did poorly at scene recognition.

Turning to the concurrent discrimination tasks, our fornix patients were no less impaired than the amnesics with hippocampal or thalamic pathology. This conflicts with the studies on monkeys, cited in the Introduction, which reported little or no impairment of concurrent object discrimination learning after fornix transection, but substantial deficits after hippocampectomy or dorsomedial thalamus ablation.

Further inconsistency between the human and animal results appears when we examine the results of the computer-presented pattern discriminations in more detail. The procedure employed therein, with spatially contiguous visual feedback for correct choices, was derived from the study (Gaffan *et al.*, 1989) which found that monkeys could still learn discriminations of this kind rapidly after amygdalectomy combined with fornix transection, at least when pairs were presented sequentially. By contrast, Gaffan *et al.* (1990) found that Korsakoff amnesics showed a lasting impairment in learning such pattern discriminations, whether concurrently or sequentially. The less severely amnesic subjects of the present study were, likewise, stably impaired in concurrent pattern (and object) discriminations at the end of the training sequence.

Gaffan *et al.* (1990) noted, however, that although controls usually learned more rapidly than Korsakoff patients, there was an intermediate stage of practice at which the learning rate of the two groups was identical, namely during the second, 6-pair concurrent problem of a 3-problem sequence similar to that which the present subjects learned. The results obtained here were somewhat similar in that the amnesics were less impaired on the second concurrent set than on any other.

There are several possible interpretations of the nonmonotonic pattern of intergroup differences across the 3 problems. One hypothesis is that amnesics are impaired at first partly because they are slow to acquire the principle of the task, as noted by Squire *et al.* (1988). Having done so, in the course of learning the easy first problem, they are relatively less impaired on the second. To explain their eventual more consistent deficit it must be supposed that the controls later develop a more sophisticated strategy, less available to the amnesics. Both in the present study and in the earlier one with Korsakoff amnesics, the controls learned the third, 10-pair problem faster than they did the preceding, theoretically easier, 6-pair one, which is consistent with a change of strategy. There are, however, other possibilities. The results could be an artefact of the particular sequence of stimuli we used, as the order was not counterbalanced; or they could reflect a deficiency peculiar to the controls, such as a build-up of proactive interference. The former is made less plausible by the fact that we found a similar profile of results in the 2 studies despite using different subject populations, stimuli and procedural details. The latter is questionable because proactive interference would be expected to affect the final problem as much or more than the second, yet the controls excelled more clearly on the third than on the second set. We cannot decide between these possibilities without carrying out a more elaborate series of experiments.

Whatever the correct explanation of the nonmonotonic deficit, it is undeniably different from any reported effects of brain lesions in monkeys. Experiments which gave monkeys a series of 3 or more concurrent discrimination problems of similar difficulty (Malamut *et al.*, 1984) or progressively increasing difficulty (Correll and Scoville, 1965) found that the deficit generated by medial temporal or dorsal thalamic lesions was stable or declined across problems with the former procedure, and progressively worsened with the latter. It is possible, of course, that a nonmonotonic effect would appear if monkeys were given a longer sequence of problems, or if their initial level of naivete was varied, but we can only speculate at present.

Gaffan *et al.* (1990) noted further aspects of the deficit in discrimination learning shown by Korsakoff patients which did not resemble that seen in monkeys with large medial temporal lesions. They suggested that the presence of dorsomedial thalamic lesions in Korsakoff patients might explain their pervasive impairments. If so, we can understand why Cases 4 and 5 (who had thalamic lesions) had difficulty with discrimination learning, but it is still unclear why Case 5 and the 2 fornix cases were so impaired.

Thus both in this and our previous study we found some inconsistencies between the performance of amnesic patients and monkeys with supposedly equivalent lesions when tested on analogous tasks. There seem to be 3 possible, not mutually exclusive, conclusions. (1) The patients did not in fact have brain lesions similar to those of the animal with which they are being compared. (2) The performance of human subjects is affected by features 'incidental' to the basic memory deficit which have no analogue in animals, such as anxiety or motivational states induced when they are conscious that they have a memory problem and that their memory is being tested. (3) The tasks, while ostensibly the same, are solved differently by the 2 species and therefore may not depend on the same brain structures.

The first idea, nonequivalence of lesions, may well apply to Korsakoff or postencephalitic amnesics who, unlike the monkeys in the corresponding studies, often have widespread damage extending to the frontal cortex, for example. It is less relevant to the present study where the patients had restricted lesions with no evidence of disseminated cortical damage. The second idea is plausible, and may explain why some of our subjects' impairments were excessive; but it cannot be the whole story, for 3 of them performed normally at one of the memory tests, delayed matching to sample. The third account is the most likely. The discrimination tasks we used were designed for animals and could in theory be treated as purely visual, that is, 'identify which visual stimuli are associated with flashing/the sight of a marble'. However, not only from the restrospective comments of the subjects, but from the fact that some of our patients were impaired despite having near normal 'nonverbal' memory, it appears that most people try to remember the stimuli by descriptive labelling, a strategy which is qualitatively different from any available to animals.

Any of the above reasons may account for the fact that we did not detect different patterns of impairment in patients with anatomically distinct lesions. In view of the above-mentioned problems inherent in trying to test humans and animals on the 'same' task, we conclude that it will be necessary to use more subtle analytic tests designed separately for humans and animals, rather than attempt to mimic 'animal' tasks for people, if we wish to detect such functional separation.

Finally, our demonstration of moderate but wide-ranging memory deficits following fornix transection adds to the growing evidence (Geffen *et al.*, 1980; Tucker *et al.*, 1988) that such damage alone can cause a disabling memory impairment. There are, however, also negative reports where fornix transection had no noticeable effect on memory (*see* Horel, 1978; Parkin, 1984; Garcia-Bengochea and Friedman, 1987). These reviewers have proposed that the positive reports of memory loss following fornix damage can be otherwise accounted for, by extrafornical damage, generalized dementia or (in the case of patients with colloid cysts) effects of raised intraventricular pressure antedating cyst removal. None of these counter-explanations plausibly applies to the 2 present fornix cases. There were no clinically apparent cognitive changes before operation, and full neuropsychological assessment postoperatively showed the cognitive deficit to be confined to memory function. Furthermore, imaging studies offered no evidence of extrafornical damage. On the basis of these and the other positive findings mentioned above, we would argue that the real problem is to explain why fornix transection sometimes reportedly has no effect, rather than why it sometimes does.

Most amnesics have suffered damage not only to the pathway from the hippocampus via the fornix to the mamillary bodies and anterior thalamus, but also to the amygdalo-dorsal thalamus pathway, and it has been argued that severe amnesia, in man or monkey, occurs only if both pathways are defective (Victor *et al.*, 1971; Mishkin, 1982). Amnesia resulting from fornix section is therefore of particular interest because it allows us to study the effect of a lesion confined to the hippocampal system. Such selective damage is rare except in experimental work with animals. Careful analysis of such cases, and comparison with similar lesions in monkeys, will help to elucidate the separate contributions of the hippocampus and other structures to human memory.

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REFERENCES

AGGLETON JP (1986) Memory impairments caused by experimental thalamic lesions in monkeys. *Revue Neurologique*, **142**, 418–424.

AGGLETON JP, NICOL RM, HUSTON AE, FAIRBAIRN AF (1988) The performance of amnesic subjects on tests of experimental amnesia in animals: delayed matching-to-sample and concurrent learning. *Neuropsychologia*, **26**, 265–272.

BACHEVALIER J, PARKINSON JK, MISHKIN M (1985) Visual recognition in monkeys: effects of separate vs. combined transection of fornix and amygdalofugal pathways. *Experimental Brain Research*, **57**, 554–561.

BRIERLEY JB (1977) Neuropathology of amnesic states. In: *Amnesia: Clinical, Psychological and Medicolegal Aspects*. Second edition. Edited by C. W. M. Whitty and O. L. Zangwill. London: Butterworths, pp. 199–223.

CAIRNS H, MOSBERG WH (1951) Colloid cyst of the third ventricle. *Surgery, Gynecology and Obstetrics*, **92**, 545–570.

CAMERON AS, ARCHIBALD YM (1981) Verbal memory deficit after left fornix removal: a case report. *International Journal of Neuroscience*, **12**, 201.

CARMEL PW (1985) Tumours of the third ventricle. *Acta Neurochirurgica*, **75**, 136–146.

CHRISTIANSEN JC (1970) Discussion of paper by K. Sugita *et al.* In: *Special Topics in Stereotaxis: Epilepsy, Disorders of Behaviour, and Autonomic Balance.* Edited by W. Umbach. Stuttgart: Hippokrates, p. 51.

CLARK CR, GEFFEN GM (1989) Corpus callosum surgery and recent memory: a review. *Brain*, **112**, 165–175.

CORRELL RE, SCOVILLE WB (1965) Effects of medial temporal lesions on visual discrimination performance. *Journal of Comparative and Physiological Psychology*, **60**, 175–181.

GAFFAN D (1974) Recognition impaired and association intact in the memory of monkeys after transection of the fornix. *Journal of Comparative and Physiological Psychology*, **86**, 1100–1109.

GAFFAN D (1977) Monkeys' recognition memory for complex pictures and the effect of fornix transection. *Quarterly Journal of Experimental Psychology*, **29**, 505–514.

GAFFAN D, GAFFAN EA, HARRISON S (1984*a*) Effects of fornix transection on spontaneous and trained non-matching by monkeys. *Quarterly Journal of Experimental Psychology*, **36B**, 285–303.

GAFFAN D, SAUNDERS RC, GAFFAN EA, HARRISON S, SHIELDS C, OWEN MJ (1984*b*) Effects of fornix transection upon associative memory in monkeys: role of the hippocampus in learned action. *Quarterly Journal of Experimental Psychology*, **36B**, 173–221.

GAFFAN D, SHIELDS C, HARRISON S (1984*c*) Delayed matching by fornix-transected monkeys: the sample, the push and the bait. *Quarterly Journal of Experimental Psychology*, **36B**, 305–317.

GAFFAN D, SAUNDERS RC (1985) Running recognition of configural stimuli by fornix-transected monkeys. *Quarterly Journal of Experimental Psychology*, **37B**, 61–71.

GAFFAN D, GAFFAN EA, HARRISON S (1989) Visual-visual associative learning and reward-association learning in monkeys: the role of the amygdala. *Journal of Neuroscience*, **9**, 558–564.

GAFFAN D, HARRISON S (1989) Place memory and scene memory: effects of fornix transection in the monkey. *Experimental Brain Research*, **74**, 202–212.

GAFFAN EA, AGGLETON JP, GAFFAN D, SHAW C (1990) Concurrent and sequential pattern discrimination learning by patients with Korsakoff amnesia. *Cortex*, **26**, 381–397.

GARCIA-BENGOCHEA F, FRIEDMAN WA (1987) Persistent memory loss following section of the anterior fornix in humans: a historical review. *Surgical Neurology*, **27**, 361–364.

GEFFEN G, WALSH A, SIMPSON D, JEEVES M (1980) Comparison of the effects of transcortical and transcallosal removal of intraventricular tumours. *Brain* **103**, 773–788.

HODGES JR, CARPENTER K (1991) Selective anterograde amnesia following the removal of a IIIrd ventricle colloid cyst: a study of 2 cases. *Journal of Neurology, Neurosurgery and Psychiatry*, In press.

HODGES JR, WARD CD (1989) Observations during transient global amnesia: a behavioural and neuropsychological study of five cases. *Brain*, **112**, 595–620.

HOREL JA (1978) The neuroanatomy of amnesia: a critique of the hippocampal memory hypothesis. *Brain*, **101**, 403–445.

JEEVES MA, SIMPSON DA, GEFFEN G (1979) Functional consequences of the transcallosal removal of intraventricular tumours. *Journal of Neurology, Neurosurgery and Psychiatry*, **42**, 134–142.

MAHUT H, ZOLA-MORGAN S, MOSS M (1982) Hippocampal resections impair associative learning and recognition memory in the monkey. *Journal of Neuroscience*, **2**, 1214–1229.

MAIR WGP, WARRINGTON EK, WEISKRANTZ L (1979) Memory disorder in Korsakoff's psychosis: a neuropathological and neuropsychological investigation of two cases. *Brain*, **102**, 749–783.

MALAMUT BL, SAUNDERS RC, MISHIKIN M (1984) Monkeys with combined amygdalo-hippocampal lesions succeed in object discrimination learning despite 24-hour intertrial intervals. *Behavioral Neuroscience*, **98**, 759–769.

MILNER B (1972) Disorders of learning and memory after temporal lobe lesions in man. *Clinical Neurosurgery*, **19**, 421–446.

MISHKIN M (1982) A memory system in the monkey. *Philosophical Transactions of the Royal Society of London, B*, **298**, 85–95.

MOSS M, MAHUT H, ZOLA-MORGAN S (1981) Concurrent discrimination learning of monkeys after hippocampal, entorhinal, or fornix lesions. *Journal of Neuroscience*, **1**, 227–240.

NELSON HE (1982) *National Adult Reading Test*. Windsor: NFER-Nelson.

NITTA M, SYMON L (1985) Colloid cysts of the third ventricle: a review of 36 cases. *Acta Neurochirurgica*, **76**, 99–104.

OSCAR-BERMAN M, ZOLA-MORGAN SM (1980) Comparative neuropsychology and Korsakoff's syndrome. II—Two-choice visual discrimination learning. *Neuropsychologia*, **18**, 513–525.

OWEN MJ, BUTLER SR (1981) Amnesia after transection of the fornix in monkeys: long-term memory impaired, short-term memory intact. *Behavioural Brain Research*, **3**, 115–123.

PARKIN AJ (1984) Amnesic syndrome: a lesion-specific disorder? *Cortex*, **20**, 479–508.

POPPEN JL, REYES V, HORRAX G (1953) Colloid cysts of the third ventricle: report of seven cases. *Journal of Neurosurgery*, **10**, 242–263.

SQUIRE LR, ZOLA-MORGAN S, CHEN KS (1988) Human amnesia and animal models of amnesia: performance of amnesic patients on tests designed for the monkey. *Behavioral Neuroscience*, **102**, 210–221.

SWEET WH, TALLAND GA, ERVIN FR (1959) Loss of recent memory following section of fornix. *Transactions of the American Neurological Association*, **84**, 76–82.

TUCKER DM, ROELTGEN DP, TULLY R, HARTMANN J, BOXELL C (1988) Memory dysfunction following unilateral transection of the fornix: a hippocampal disconnection syndrome. *Cortex*, **24**, 465–472.

VALENSTEIN E, BOWERS D, VERFAELLIE M, HEILMAN KM, DAY A, WATSON RT (1987) Retrosplenial amnesia. *Brain*, **110**, 1631–1646.

VICTOR M, ADAMS RD, COLLINS GH (1971) *The Wernicke-Korsakoff Syndrome: A Clinical and Pathological Study of 245 Patients, 82 with Post-Mortem Examinations*. Oxford: Blackwell and Philadelphia: F. A Davis.

ZOLA-MORGAN S, SQUIRE LR (1985) Amnesia in monkeys after lesions of the mediodorsal nucleus of the thalamus. *Annals of Neurology*, **17**, 558–564.

ZOLA-MORGAN S, SQUIRE LR, AMARAL DG (1989) Lesions of the hippocampal formation but not lesions of the fornix or the mammillary nuclei produce long-lasting memory impairment in monkeys. *Journal of Neuroscience*, **9**, 898–913.

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EYE MOVEMENT BEHAVIOUR OF PATIENTS WITH CEREBRAL MICROANGIOPATHY AND MACROANGIOPATHY IN SIMPLE VISUAL DETECTION TASKS

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SUMMARY

Patients with cerebral microangiopathy (n = 17), acute and chronic left hemisphere (LH) stroke (n = 18, n = 21) and normal controls (n = 41) were studied in 2 simple visual detection tasks, one with predictable, the other with unpredictable targets. Eye movements were registered by means of infrared light reflections (pupil-corneal reflection method); the points of visual fixation were continuously calculated by a microprocessor system. Patients with cerebral microangiopathy showed primarily difficulties in holding attention, as reflected by pathologically short durations of gaze on target, frequent unsuccessful anticipations and a high overall number of fixations. In contrast, acute LH stroke patients were characterized by a deficit in shifting attention, as reflected by prolonged latencies and long search durations due to many intervening search fixations. By means of a nonparametric discriminant analysis procedure, about 90% of patients with microangiopathy and about 80% of acute LH stroke patients were reliably distinguished from normal controls. The differences between these two patient groups were most pronounced in the simpler task with predictable targets. Among those patients discriminated from normals, about 96% were correctly reclassified as belonging either to the microangiopathy or to the acute LH stroke group on the basis of their abnormal eye movement variables alone.

INTRODUCTION

In recent years, several studies of oculomotor behaviour have attempted to characterize the neurological deficits in brain-damaged patients (Jenkyn *et al.*, 1977; Hershey *et al.*, 1983; Leigh *et al.*, 1983; Bronstein and Kennard, 1985; Fletcher and Sharpe, 1986; Hotson and Steinke, 1988). The standard experimental paradigm makes use of simple saccadic tasks that require the subject to look at sequentially illuminated targets (LEDs). Two variables were found to be of great importance: saccadic latency and stability of fixation (Meienberg, 1988).

Prolonged latencies in combination with impersistence of gaze are thought to reflect cortical impairment as the symptoms co-occur in Alzheimer's disease (Fletcher and Sharpe, 1986; Hotson and Steinke, 1988). In the present study we examined this claim further by contrasting two neurological groups which have not been examined so far. These were patients with subcortical involvement due to cerebral microangiopathy as opposed to stroke patients with circumscribed cortical lesions within the distribution area of the left middle cerebral artery (MCA). Among the stroke patients we distinguished

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acute and chronic cases in order to discover to what extent permanent deficits of eye movement behaviour may occur after cortical infarct.

Besides visual detection and oculomotor response, any saccadic task is likely to impose attentional demands. Recent electrical stimulation studies in monkeys have shown that latency and amplitude of saccades depend on whether the monkey is in a state of active attentive fixation, or in a state of passive resting fixation. In the first case higher thresholds and smaller sacccadic amplitudes were found. This was reported from stimulating posterior parietal cortex (Shibutani *et al.*, 1984) as well as frontal eye fields (Schiller and Sandell, 1983; Goldberg *et al.*, 1986). Mesulam (1981) gave persuasive arguments for the view that orienting attention is best understood in terms of a neural network system connecting posterior parietal, limbic and frontal areas of each hemisphere. Within an information processing perspective, Posner and Rafal (1987) distinguished three elementary mental operations of orienting attention: disengagement, shifting and engagement.

In conditions of cortical and subcortical brain damage, we expect the presence of abnormal eye movement behaviour despite absence of visual and/or oculomotor deficits on clinical examination. On the behavioural level such abnormalities are best described as attentional deficits. Instability of fixation in combination with inability to suppress anticipatory saccades are then the result of deficits in holding attention, whereas prolongation of latencies, lack of successful anticipations and prolonged search for a new target reflect deficits of either disengagement or shifting attention.

A further critical finding would be hypometric saccades, that is, moving the gaze towards a new target in a sequence of several short saccades. This symptom is generally assumed to be characteristic for oculomotor and/or attentional deficits, particularly in patients with visual hemifield deficits (Meienberg *et al.*, 1981, 1986; Girotti *et al.*, 1983; Huber *et al.*, 1988). Our experience with an eye tracking system that calculates points of visual fixation on-line (pupil-corneal reflection method, *cf* Young and Sheena, 1975) led us to assume that so-called hypometric saccades frequently reflect sequences of attempts to shift the gaze to the new target. These attempts are characterized by a scanpath with one or several interrupting fixations and with saccadic steps that repeatedly change direction, thereby gradually approaching the new target. Thus hypometric saccades most likely reflect difficulties in shifting attention.

In short, in this study we wished to discover whether patients with cerebral microangiopathy in contrast to those with macroangiopathy (acute and chronic left middle cerebral artery (MCA) stroke patients) differ with respect to eye movement variables that reflect either differences in holding or in shifting attention. We wondered to what extent these three clinical groups of patients can be statistically distinguished on the basis of eye movement measures alone.

METHODS

Procedure

The subjects had to carry out 2 tasks. In the predictive task they were asked to fixate 2 light-emitting diodes (LEDs) which were arranged horizontally at a distance of 16° visual angle. The task lasted for 2 min during which 80 LED alternations occurred. The single LED was always switched on for 1.5 s.

In the nonpredictive task, the subjects were required to look at a central fixation point on the screen with 20 peripheral LEDs regularly distributed in a 4×5 lattice with a vertical and horizontal distance of 8° between. Each of the peripheral LEDs was illuminated for 5 s in a quasirandom order.

Registration technique

The subjects were seated with their head slightly fixed at a distance of 175 cm away from the screen (75 cm high × 100 cm wide). For calibration the subject had to fixate the 20 peripheral LEDs. During calibration and succeeding registration, the laboratory was completely darkened. The LEDs (2.2 V, 20 mA) had a constant luminance. Their colour was white except for the central fixation point, which was red.

Eye movements were recorded with the pupil-corneal reflection method. The subject's eye was illuminated by invisible infrared light, and the reflections were viewed by a video camera. On the basis of the preceding calibration, the subject's points of regard were continuously calculated by tracking the corneal reflection with respect to the pupil centre. The apparatus consisted of a DEBIC 84 microprocessor system (Demel Microcomputer GMBH, Haan, Germany) which was used with a conventional video system. The LEDs were built into the projection screen and were triggered via the microcomputer.

The system took 25–50 measurements/s. The mean euclidian accuracy was 0.07° of visual angle with an SD of 1.6° (based on 2721 fixations of 18 students measured on the 20 peripheral LEDs).

Data reduction was achieved by a modified version of the program EMAN (Kliegl, 1981). Successive measurement points were combined into 'fixations' as long as they fell into a gliding window of 2° of visual angle. The minimum duration of fixations was set at 30 ms.

Subjects

The sample characteristics of the 5 subject groups are given in Table 1. Besides 2 groups of normal controls, the study included 3 groups of brain-damaged patients with no clinical signs of gaze paralysis, visual field defect and/or visual hemineglect. There were 2 groups of left hemisphere (LH) stroke patients with circumscribed brain lesions in MCA distribution as assessed by cranial computed tomography (CT). In 18 patients, the brain damage was acute, that is, with a duration of less than 4 wks. In 21 patients, the duration extended over at least 3 mos. In a third group of 17 neurological patients, the clinical diagnosis was small vessel disease (cerebral microangiopathy) as opposed to large vessel disease with consecutive territorial infarcts. This diagnosis was primarily based on a history of 'little strokes' with arterial hypertension and CT findings demonstrating for each patient the presence of multiple lacunes, white matter attenuation or both (*cf* Zeumer *et al.*, 1980; Schneider, 1988).

Because of the clinical selection, distribution of sex and age was variable across patient groups. Initially we considered 2 normal control groups, with young and elderly subjects. As they did not differ significantly in any of the eye movement parameters considered (t tests, $\alpha = 5\%$), the control groups were collapsed.

In all subjects, visual acuity of the examined eye was at least 0.4. In 12 subjects, vision was corrected; they were wearing glasses during the recording. Eye movements were recorded from the dominant right eye in 71 subjects, from the dominant left in 12 subjects and from the nondominant left eye in 14 subjects. Eye dominance was tested by a procedure described by Porac and Coren (1981).

TABLE 1 SAMPLE CHARACTERISTICS OF PATIENTS AND CONTROLS

		Sex			
	n	*F*	*M*	*Age (yrs)**	*Duration*
LH stroke					
Acute	18	10	8	57.7 (14.7)**	7 days (3–20)
Chronic	21	15	6	49.0 (12.6)**	24 mos (3–63)
Cerebral microangiopathy	17	6	11	69.1 (9.6)	Uncertain
Controls					
Elderly	20	9	11	57.0 (7.1)**	–
Young	21	10	11	25.1 (3.3)	–

* Mean, SD in brackets ** No significant difference with respect to age (type I error = 5%, t test).

Dependent variables

We calculated 3 time variables: latency, search duration and duration of gaze on target. Latency was defined as the time span between illumination of a new target and disengagement of gaze from a preceding target, i.e., only positive values (>0) were considered. Search duration was the time span between disengagement of gaze and onset of gaze on the new target.

The following frequency variables were also considered: overall number of fixations, number of fixations during search, as well as number of anticipations. In the predictive task, anticipations were further classified into successful and unsuccessful. With unsuccessful anticipations, the subject moved randomly away from the LED while it was still illuminated, thus reducing the duration of gaze on target. With successful anticipations, the subject made a predictive eye movement to the approximate location of the succeeding target.

RESULTS

In the first step of the analysis we determined the proportion of patients that could reliably be distinguished from normal controls. This was achieved by means of a nonparametric discriminant analysis procedure (ALLOC 80, Hermans *et al.*, 1982). We considered time and frequency variables separately in order to have a reasonable relation between sample sizes and number of dependent variables. The ALLOC program allows a stepwise forward selection of best discriminating variables. By using the leaving-one-out method, the ALLOC program also prevents an underestimation of the error of misclassification.

The misclassification rates of normal controls were quite small, even when compared with chronic LH stroke patients. The rates varied from 5% to 8% for time variables and from 5% to 12% for frequency variables. Poor separation was obtained for the chronic LH stroke group. As many as 43% and 52% of these patients also fell into the range of normal eye movement behaviour. Patients with microangiopathy and acute LH stroke could well be separated from normal controls, but only in the predictive task. Outstandingly short durations of gaze on target and large number of overall fixations characterized patients with microangiopathy. For these two variables, misclassification rates of only 9.5% and 12.5% were obtained. In contrast, misclassification rates for the best distinguishing variables in the acute LH stroke patients were 20.7% for search duration and 20.2% for overall number of fixations.

In the next step of the analysis we discriminated between patient groups. Only those patients were considered who were successfully distinguished from normals in the previous analyses. The best overall discrimination (96%) was obtained between patients with cerebral microangiopathy and those with acute LH stroke. Four of the variables accounted for their separation. They are listed in Table 2, which also gives the mean values of the total group of normal controls (n = 41).

On the one hand, duration of gaze on target was outstandingly short in patients with cerebral microangiopathy and they made the highest number of unsuccessful anticipations (*see* Table 2). On the other hand, acute LH patients showed more prolonged latencies and a higher number of search fixations, indicating hypometric and corrective saccades. Based on these findings, patients with cerebral microangiopathy appear to have difficulty in holding attention, and acute LH stroke patients in shifting attention.

Patients with cerebral microangiopathy and those with chronic LH stroke could be less well separated. Only 71% were distinguished on the basis of number of unsuccessful anticipations, which were outstandingly frequent in 8 patients with cerebral micro-

TABLE 2 PREDICTIVE TASK MEAN VALUES AND SDs OF SELECTED VARIABLES FOR SUCCESSFULLY DISCRIMINATED PATIENTS AND FOR THE TOTAL GROUP OF NORMAL CONTROLS

Selected variable *($\bar{x}$ (SD) of normals, n = 41)*	*Microangiopathy* *(n′ = 13 (76%))**	*Acute stroke* *(n′ = 11 (61%))**	*t test* *two-tailed*
Latency (ms) (218 (53))	213 (32)	306 (65)	*P* = 0.001
Unsuccessful anticipations (14 (13))	41 (13)	19 (14)	*P* = 0.001
Duration of gaze on target (ms) (1377 (61))	975 (178)	1206 (235)	*P* = 0.015
Search fixations (0.13 (0.11))	0.47 (0.21)	0.75 (0.39)	*P* = 0.53
	Microangiopathy *(n′ = 8 (47%))**	*Chronic stroke* *(n′ = 9 (43%))**	
Unsuccessful anticipations	49 (8)	27 (12)	*P* = 0.001
	Acute stroke *(n′ = 8 (44%))**	*Chronic stroke* *(n′ = 9 (43%))**	
Latency (ms)	328 (63)	216 (22)	*P* = 0.001

* Proportion of the clinically selected group after discriminant analysis.

angiopathy but only in 1 chronic LH stroke patient. Additional consideration of any other variable did not lead to a better separation, that is, both groups were similarly affected.

Finally, acute and chronic LH stroke patients could be distinguished in 81% of the cases on the basis of latency alone which was outstandingly long in 8 patients in the acute stage but only in 1 chronic patient. It therefore appears that the initial difficulties of shifting attention decrease during recovery from left MCA stroke.

In the nonpredictive task, the separation between patient groups was much wider than in the predictive task. Only between 61% and 73% of the patients compared were correctly reclassified. Most remarkable was the poor distinction between patients with cerebral microangiopathy and acute LH stroke (61%), who were best separated in the predictive task. Obviously, the nonpredictive task was less useful to characterize specific pathological deviations in eye movement behaviour of the patient groups selected.

Even when considering only those few patients successfully discriminated and comparing their mean values of selected variables, only one significant difference was found. The duration of gaze on target was significantly shorter in patients with cerebral microangiopathy ($n' = 6$, $\bar{x} = 1517$ ms, SD = 301) than in chronic LH stroke patients ($n' = 6$, $\bar{x} = 2652$ ms, SD = 707; $P = 0.009$).

DISCUSSION

In the predictive task, patients with cerebral microangiopathy showed outstandingly pathological behaviour. They appeared to be hyperreactive as their behaviour was characterized by a very marked decrease of duration of gaze on target which remained reduced throughout the whole task. Instead of keeping the eye on the target, they were repeatedly engaged in random fixations all over the projection screen. This contributed mainly to their high overall number of fixations. Furthermore, they made more unsuccessful anticipations than any of the other 2 patient groups. The underlying difficulty appears to be a deficit in holding attention on an illuminated target.

The results for latencies found in the predictive task were rather surprising. Only after acute stroke, we found low speed of reaction, whereas the latencies of patients with microangiopathy remained within the normal range.

The eye movement abnormalities found for cerebral microangiopathy were strikingly similar to those reported for patients with Alzheimer's disease (Fletcher and Sharpe, 1986). These patients also showed normal latencies for predictable targets but prolonged latencies for unpredictable targets. The main symptom of these patients was instability of gaze in all task conditions. This was also true for the patients with cerebral microangiopathy in our study, as reflected by their outstandingly short durations of gaze on target. Therefore, the claim of Fletcher and Sharpe that disturbed fixation behaviour is due to impaired cortical function has to be expanded. Subcortical white matter dysfunction (being the main factor in cerebral microangiopathy) likewise affects the control of fixation. Thus our findings support the view that in diffuse and progressive brain damage a distinction between cortical and subcortical dysfunction is questionable when extended to the behavioural level (*see* Huber *et al.*, 1986; Whitehouse, 1986).

The long latencies of acute LH stroke patients, even with highly predictable targets, most likely indicate difficulties in oculomotor programming. Despite prolonged preparation of saccades, the subsequent eye movements were far from optimal in finding the target. They showed long search durations due to many intervening search fixations. It is worth stressing that the main problem in patients with cerebral microangiopathy, namely their outstanding instability of fixation, does not seem to lead to apparent programming difficulties to a great extent when targets are predictable. Otherwise they should be as disturbed in their search variables as the acute LH stroke patients. In behavioural terms, impairment in holding attention is due to different underlying mechanisms compared with impaired shifting of attention.

After stroke in the left MCA territory, the characteristic eye movement symptoms in the initial stage disappear during recovery. Chronic LH patients after 3 mos postonset do not continue to show difficulties in shifting attention as reflected by long latencies before the eye moves to a new target. Subnormal latencies appear to be a valid indicator of residual attentional deficits during recovery after left MCA stroke.

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REFERENCES

BRONSTEIN AM, KENNARD C (1985) Predictive ocular motor control in Parkinson's disease. *Brain*, **108**, 925–940.

FLETCHER WA, SHARPE JA (1986) Saccadic eye movement dysfunction in Alzheimer's disease. *Annals of Neurology*, **20**, 464–471.

GIROTTI F, CASAZZA M, MUSICCO M, AVANZINI G (1983) Oculomotor disorders in cortical lesions in man: the role of unilateral neglect. *Neuropsychologia*, **21**, 543–553.

GOLDBERG ME, BUSHNELL MC, BRUCE CJ (1986) The effect of attentive fixation on eye movements evoked by electrical stimulation of the frontal eye fields. *Experimental Brain Research*, **61**, 579–584.

HERMANS J, HABBEMA JDF, KASANMOENTALIB TKD, RAATGEVER JW (1982) *ALLOC 80 – Discriminant Analysis Program:* The Netherlands: University of Leiden.

HERSHEY LA, WHICKER L, ABEL LA, DELL'OSSO LF, TRACCIS S, GROSSNIKLAUS D (1983) Saccadic latency measurements in dementia. *Archives of Neurology, Chicago*, **40**, 592–593.

HOTSON JR, STEINKE GW (1988) Vertical and horizontal saccades in aging and dementia. *Neuro-ophthalmology*, **8**, 267–273.

HUBER SJ, SHUTTLEWORTH EC, PAULSON GW, BELLCHAMBERS MJG, CLAPP LE (1986) Cortical vs subcortical dementia: neuropsychological differences. *Archives of Neurology, Chicago*, **43**, 392–394.

HUBER W, GUILLOT G, KARNATH H-O (1988) Blickbewegungsstrategien beim Lesen mit linksseitiger Hemianopsie und Hemineglect. *Zeitschrift für Klinische Psychologie*, **17**, 244–259

JENKYN LR, WALSH DB, CULVER CM, REEVES AG (1977) Clinical signs in diffuse cerebral dysfunction. *Journal of Neurology, Neurosurgery and Psychiatry*, **40**, 956–966.

KLIEGL R (1981) Automated and interactive analysis of eye fixation data in reading. *Behavior Research Methods and Instrumentation*, **13**, 115–120.

LEIGH RJ, NEWMAN SA, FOLSTEIN SE, LASKER AG, JENSEN BA (1983) Abnormal ocular motor control in Huntington's disease. *Neurology, Cleveland*, **33**, 1268–1275.

MEIENBERG O (1988) *Sakkadische Augenbewegungen in der Neurologischen und Ophthalmologischen Diagnostik.* Berlin: Springer.

MEIENBERG O, ZANGEMEISTER WH, ROSENBERG M, HOYT WF, STARK L (1981) Saccadic eye movement strategies in patients with homonymous hemianopia. *Annals of Neurology*, **9**, 537–544.

MEIENBERG O, HARRER M, WEHREN C (1986) Oculographic diagnosis of hemineglect in patients with homonymous hemianopia. *Journal of Neurology*, **233**, 97–101.

MESULAM M-M (1981) A cortical network for directed attention and unilateral neglect. *Annals of Neurology*, **10**, 309–325.

PORAC C, COREN S (1981) *Lateral Preferences and Human Behavior.* New York: Springer

POSNER MI, RAFAL RD (1987) Cognitive theories of attention and the rehabilitation of attentional deficits. In: *Neuropsychological Rehabilitation.* Edited by M. J. Meier, A. L Benton and L. Diller. Edinburgh: Churchill Livingstone, pp. 182–201.

SCHILLER PH, SANDELL JH (1983) Interactions between visually and electrically elicited saccades before and after superior colliculus and frontal eye field ablations in the rhesus monkey. *Experimental Brain Research*, **49**, 381–392.

SCHNEIDER R (1988) *Epidemiologie und Pathophysiologie Zerebraler Mikroangiopathien, Habilitationsschrift.* RWTH Aachen (unpublished).

SHIBUTANI H, SAKATA H, HYVÄRINEN J (1984) Saccade and blinking evoked by microstimulation of the posterior parietal association cortex of the monkey. *Experimental Brain Research*, **55**, 1–8.

WHITEHOUSE PJ (1986) The concept of subcortical and cortical dementia: another look. *Annals of Neurology*, **19**, 1–6.

YOUNG LR, SHEENA D (1975) Survey of eye movement recording methods. *Behavior Research Methods and Instrumentation*, **7**, 397–429.

ZEUMER H, SCHONSKY B, STURM KW (1980) Predominant white matter involvement in subcortical arteriosclerotic encephalopathy (Binswanger disease). *Journal of Computer Assisted Tomography*, **4**, 14–19.

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STEREOPSIS AFTER UNILATERAL ANTERIOR TEMPORAL LOBECTOMY

DISSOCIATION BETWEEN LOCAL AND GLOBAL MEASURES

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SUMMARY

In man, an impairment in stereopsis may occur following damage outside the occipital lobes. If local and global stereopsis can be dissociated, this may imply that different mechanisms mediate these functions. We tested 44 patients with unilateral anterior temporal lobe excisions and 23 normal control subjects on two tasks. In the local stereopsis task, subjects indicated which of two pins varying in disparity between 4 and 512 s of arc was closer. Results showed no threshold impairment in any group. In the global stereopsis task, random-dot stereograms varying in binocular correlation were presented in random order, and subjects indicated if the squares perceived in depth were in front of or behind the screen. At binocular correlations between 50% and 70%, left and right temporal lobectomy resulted in a deficit, which was more marked following right-sided excisions. These results are concordant with earlier work (Ptito and Zatorre, 1988), and with other evidence of a right hemisphere superiority in treating binocular depth information. Moreover, the fact that global stereopsis is impaired in the presence of intact local stereopsis suggests that closely related but not identical mechanisms are involved, and fits the notion that there is a hierarchical organization of the visual pathways originating in the striate cortex leading into temporal cortex. Global stereopsis would thus be mediated in temporal lobe areas that receive information about local disparities from more posterior regions.

INTRODUCTION

Julesz (1971), using random-dot stereograms (RDS), has demonstrated that stereoscopic depth can be perceived in the absence of monocular cues, and that two separate mechanisms, one local and one global, can be differentiated. Julesz (1978) refers to local stereopsis as localization of depth of feature elements whose correspondence is unambiguous, and to global stereopsis as a higher-order mechanism needed for form perception that depends upon the matching of corresponding clusters of elements found among many other possible clusters. Despite this improved knowledge of the psychophysics of stereopsis, its neural substrate remains unclear. The existence of two separate stereoscopic mechanisms raises the possibility that they may be dissociable as a consequence of different cerebral lesions.

A number of experimental studies carried out with monkeys and humans have attempted to establish the contribution of different regions of the cerebral hemispheres to the

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processing of binocular depth information. In the monkey, Cowey and Porter (1979) reported that bilateral lesions in inferior temporal cortex impaired global stereopsis, whereas removal of those portions of V1 and V2 concerned with central vision elevated stereoacuity thresholds, leaving global stereopsis intact. In another study, Cowey (1985) confirmed the deficit in global stereopsis after bilateral IT cortex lesion but he also found that the lesions impaired stereoacuity.

Studies in humans with brain damage have also yielded contradictory evidence with respect to stereopsis. Bilateral damage to the primary visual cortices and their association areas has been associated with a loss of the experience of three-dimensional vision, the deficit being so severe that the patient describes the visual scene as flat (Riddoch, 1917; Holmes and Horrax, 1919). Global stereopsis has been found to be more impaired after right than after left hemisphere lesions in several studies (Carmon and Bechtoldt, 1969; Benton and Hécaen, 1970), and Hamsher (1978) has confirmed this finding, reporting that patients with right cerebral hemisphere damage had a selective impairment of global stereopsis along with intact local stereopsis. This dissociation between local and global stereoscopic mechanisms was not confirmed by Ross (1983), who found that patients with right posterior lesions experienced deficits in both types of stereopsis. Several reports have challenged the reported right hemisphere superiority in stereopsis. Rothstein and Sacks (1972) found more severe impairments after left parietal lobe damage than after right parietal lobe lesions. In contrast, Lehmann and Wälchli (1975) attributed stereoscopic deficits in patients with right hemisphere insults to a generalized cognitive impairment rather than to a specific perceptual disturbance, thus raising another possible explanation for the deficits observed.

The patients who participated in the studies cited above rarely formed a homogeneous sample and the locus and aetiology of the lesions were often not clear or were variable. In order to address this latter point, we evaluated global stereopsis by presenting RDS varying in binocular correlation to patients with well-documented cortical excisions (Ptito and Zatorre, 1988). Results indicated that either left or right anterior temporal lobectomy, which included partial removal of the third temporal gyrus, led to higher than normal detection thresholds for RDS. In contrast, right frontal lobectomy did not have a significant effect on stereopsis.

Methodological factors may account for some of the discrepancies in the literature. Some investigations into the brain mechanisms underlying stereopsis have made use of global (Benton and Hécaen, 1970) and/or local stereograms (Rothstein and Sacks, 1972; Hamsher (1978), and others (Ross, 1983) using the TNO (Walraven, 1975) and Frisby (Sasieni, 1978; Frisby, 1980) stereoacuity tests to measure global stereoacuity, and the Keystone test (Hamsher, 1978) to measure local stereoacuity. The validity of these tests is questionable on several grounds. The TNO test uses a random-dot pattern with small densely packed dots to measure global stereoacuity. The Frisby test makes use of a random pattern of large and clearly outlined figures with a significant amount of empty space between them so that it is uncertain whether global stereopsis predominates. Furthermore, the test figure is intended to be invisible when viewed monocularly but Cooper and Feldman (1979) have shown that some observers can detect it nevertheless.

Good local stereoacuity has been defined by Westheimer and McKee (1980) as less than 10 s of arc, but the smallest disparity in the Titmus test used by Rothstein and

Sacks and Hamsher was 40 s of arc. Using this same test, Cooper and Warshowsky (1977) found that some observers could detect the smallest disparity monocularly, and therefore without stereopsis, limiting the utility of the Titmus test for measuring stereoacuity. The efficiency of the Keystone telebinocular test is also drawn into question because it is a screening test which was not intended to be used for scientific investigation. These concerns, taken together with the problems associated with the heterogeneity of the subject groups, led us to believe that the effect of focal brain damage on local stereoacuity had yet to be measured satisfactorily.

The aim of the present study was to measure local stereopsis using an automated version of Howard's (1919) two-rod apparatus, a technique that eliminates monocular cues and yields stable stereoacuity threshold estimates (Larson and Lachance, 1983; Larson, 1987, 1990). Another goal of this study was to replicate our findings on global stereopsis (Ptito and Zatorre, 1988) on a group of patients with similar lesions. We felt that this replication was necessary because in our previous study we used a method of ascending and descending limits, and differences between groups were evident only on the ascending series. In order to reduce this hysteresis effect (Julesz, 1978), in the present study we used a method of constant stimuli. Our hypothesis was that if separate brain mechanisms underlie local and global stereopsis, patients with anterior temporal lobe lesions should be impaired in global stereopsis whereas no deficit should be apparent on local stereopsis.

SUBJECTS

The experimental group was made up of 44 patients who had undergone unilateral brain surgery at the Montreal Neurological Hospital but who had not participated in our earlier study of global stereopsis (Ptito and Zatorre, 1988). All the operations had been carried out to relieve uncontrollable epileptic seizures, and most of the epileptogenic lesions were static and atrophic. Sixteen patients were seen 2 wks postoperatively and the remainder in follow-up, one or more years after the surgical intervention. A normal control group of 23 subjects chosen from patients' relatives, hospital staff and students was also tested.

Mean age and number of years of education are shown for all subjects in Table 1. Analysis of variance was performed to verify that the groups did not differ in age and education, and this was indeed found to be the case (age: F(2,58) = 0.34, education: F(2,58) = 2.40, $P = 0.10$). Full Scale IQ ratings (Wechsler Adult Intelligence Scale—Revised) are also presented in Table 1. All the patients were either known to have speech representation in the left cerebral hemisphere as determined by intracarotid sodium amytal testing, or this was presumed on the basis of dichotic listening test results, handedness and other neuropsychological test data. Patients with any evidence of strabismus as established via case history and/or neuro-ophthalmological examination were excluded.

TABLE 1 CHARACTERISTICS OF SUBJECTS TESTED*

						Extent of excision (cm)	
Group	*n*	*Age (yrs)*	*Education*	*FSIQ*	*VF loss*	*1st TG*	*3rd TG*
LT	23	29.7	13.5	101.6	10/17	4.6	5.3
RT	21	29.7	11.9	92.4	6/14	5.2	5.7
NC	23	27.9	14.0	–	–	–	–

* Mean age, mean number of years of education, mean Full Scale IQ (FSIQ), number of subjects with visual field (VF) loss out of number tested, and extent of neocortical excision along first and third temporal gyri (TG) measured from the temporal pole

Right temporal lobe group (RT)

Twenty-one patients were tested after right temporal lobectomy. The lesions comprised in all cases the amygdala, uncus, varying amounts of the hippocampus and hippocampal gyrus as well as the anterior temporal neocortex (*see* Table 1). Fourteen subjects underwent formal perimetric testing and 6 were found to have partial visual field loss in the left upper quadrant.

Left temporal lobe group (LT)

Twenty-three subjects were tested after left temporal lobectomy. The excisions were generally smaller than those in the right temporal lobe group (*see* Table 1). Of 17 patients tested on formal perimetry, 10 had a partial right upper quadrantic field defect.

METHODS

Measurement of local stereopsis

The stereoacuity test has already been described (Larson and Lachance, 1983). From a distance of 60 cm, the subject saw two vertical and parallel black lines of equal width through a window in a white screen. These lines were black rods seen in silhouette against an illuminated background. One rod was nearer to the subject than the other by the disparity to be tested. An electromechanical shutter closed the window for several seconds while the disparity was being changed. When the window opened, the subject reported which rod was nearer by means of one or two push-button switches. All monocular cues to depth were eliminated by the test's design and by immobilizing the subject's head with a head rest and forehead retainer. To ensure that no monocular cues could be used to carry out the task, subjects were briefly tested with one eye covered, but no subject was able to obtain above chance performance.

Twenty-one pairs of rods were mounted on the periphery of a disc which was turned by a stepping motor. Disparities were 512, 256, 128, 64, 32, 16, 8 and 4 s of arc, and on half the trials the left rod was nearer to the subject. To reduce testing time, presentations began at 512 s of arc and were lowered gradually if the subject obtained 3 or more correct responses out of 4. When fewer than 3 responses were correct at a given disparity, the preceding larger disparity was presented again for a total of 8 trials. This procedure was repeated at least twice in order to confirm that the disparity obtained represented a valid estimate of the subject's threshold. The stereoacuity threshold was considered to be the disparity at which the subject obtained 75% correct responses in two or more separate procedures. The probability of achieving a given stereoacuity threshold by chance alone is presented in Table 2.

TABLE 2 PROBABILITY OF ACHIEVING A GIVEN STEREOACUITY BY CHANCE ALONE

	Stereoacuity (s of arc)									
Repeats	*512*	*256*	*128*	*64*	*32*	*24*	*16*	*12*	*8*	*4*
One $P =$	0.14	0.07	0.04	0.02	0.01	0.006	0.004	0.002	0.001	0.0006
Two $P =$	0.04	0.01	0.004	0.001						
Three $P =$	0.01	0.002								

Measurement of global stereopsis

Ten RDS (red/green anaglyph form) taken from Julesz (1971; fig. 8.1–2, A–G, pp. 361–365) were photographed and mounted on slides. The stimuli were projected on a white cardboard screen via a slide projector placed 2.5 m from the subject, who wore a green filter over the left eye and a red one over the right. The stereograms differed in that the dots were systematically increased in binocular correlation from 40% to 100%. In the case of 100% correspondence, each point in one stereoimage had a corresponding point in the other and all matching points in the figure had the same disparity, which was different from the disparity in the surround. In 90% correspondence, 10% of the points were at random and the rest were correlated, and so on.

Each RDS represented two squares differing in size (9° and 6° of visual angle, respectively), such that the bigger one surrounded the smaller. The centre square of 50×50 cells is shown in an array of 100 × 100 cells. The surround has a 2-cell disparity, the centre square has a 4-cell disparity and a 10-cell margin is kept unperturbed (Julesz, 1971). The present procedure differed from our previous one (Ptito and Zatorre, 1988) in that within a single session, each slide was presented 10 times instead of twice, for a total of 70 trials intermixed in random order. On half the trials the slides were reversed, so that the squares would be perceived to be behind the screen rather than in front. Presentations were made for a maximum of 15 s, at which time subjects were required to indicate their response. To familiarize the subjects with the task 5 practice control slides depicting the concentric squares with 90% and 100% correlation described above as well as a triangle (5°), a single square (6°) and the letter T (7°) were presented twice to the subject.

RESULTS

Local stereopsis

To assess statistically the differences between the groups on local stereoscopic performance, the threshold value for each subject was entered as the dependent variable into a one-way analysis of variance. None of the differences between groups were significant (F(2,64) = 0.25), indicating that stereoacuity thresholds for all groups remained unaffected by temporal lobe excision, and were comparable with each other. Fig. 1 illustrates the mean threshold values obtained by each group of subjects.

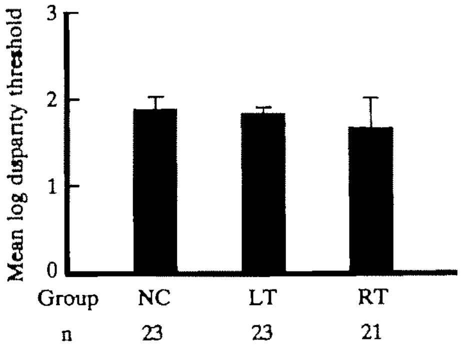

FIG 1 Local stereoacuity: mean log disparity thresholds for each subject group (error bars indicate 1 SEM)

Global stereopsis

The results observed on global stereopsis differed from those obtained on local stereopsis and are presented in fig. 2. A two-way analysis of variance was performed with Group as the between-subject factor and Binocular Correlation as the within-subject factor. This analysis yielded a significant effect of Group (F(2,64) = 5.92, $P < 0.005$) as well as a significant main effect of Binocular Correlation (F(6,384) = 200.2, $P < 0.0001$); in addition, there was a significant interaction of these two factors (F(12,384) = 3.04, $P < 0.0004$). This latter result is of greatest interest, and was examined further by means of the Neuman-Keuls post hoc procedure (Winer, 1971) to compare each group's mean performance at each level of binocular correlation. All

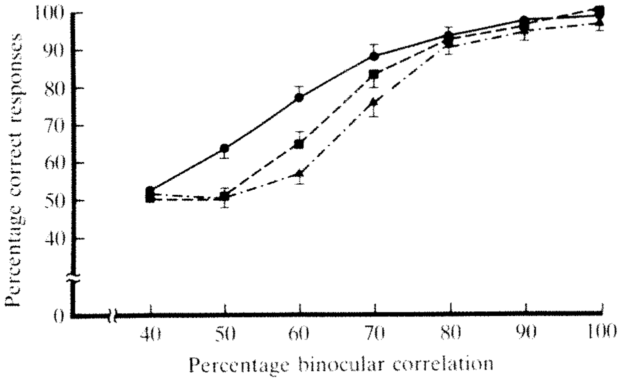

FIG. 2. Global stereopsis: percentage correct responses for each subject group as a function of binocular correlation (error bars indicate 1 SEM). Squares = LT; triangles = RT; circles = NC.

groups were able to indicate whether the squares embedded in the RDS were in front of or behind the screen when the binocular correlation between them varied from 80 to 100%, as shown by the near-ceiling performance obtained. At a correlation of 70%, the RT group differed significantly ($P < 0.05$) from the LT and NC groups. At 60% the RT group's performance was again significantly worse ($P < 0.05$) than the other two groups, but now the LT group also performed significantly more poorly ($P < 0.05$) than the normal control subjects. At 50% both temporal lobe groups experienced significantly ($P < 0.05$) more difficulty than the control group in perceiving the squares in depth. At the lowest binocular correlation (40%) all groups performed at chance levels for the detection of the depth of the square, as expected from the relatively low correspondence between the random dots (Julesz, 1971).

The dissociation between global and local stereopsis performance was examined further in two ways. First, we wished to explore the possibility that subtle deficits in local stereopsis may have been present in some patients, and that this may have influenced performance on the RDS task. Since the local stereoscopic measure yielded threshold estimates that differed by octaves (4, 8, 16 s of arc, and so on) it is possible that a slight impairment might have been missed. To exclude this possibility, we performed a subsidiary analysis in which only those subjects who obtained the lowest possible local stereoacuity threshold were retained. Application of this criterion yielded 11 subjects in the LT group, 12 in the RT group, and 11 in the NC group who obtained excellent stereoacuity thresholds of 4 s of arc. Performance of this selected set of subjects on the global stereoscopic task was then examined and the results indicated significant differences at 70% binocular correlation ($F(2,31) = 3.21$, $P = 0.05$), at 60% correlation ($F(2,31) = 5.15$, $P < 0.02$), and at 50% correlation ($F(2,31) = 4.14$, $P < 0.03$). The pattern of results was similar to that obtained for the full sample, in that the RT group again performed worse than the LT group at 60% correlation, and both patient groups were impaired at 50% binocular correlation relative to the normal control group.

Another question of interest relates to individual differences in RDS performance: although the differences between groups were clear, not all patients showed the same degree of impairment, and we wished to determine what proportion of temporal lobe patients exhibited a deficit. We therefore established a cut-off of 1 SD below the mean of the NC group, and counted how many subjects fell below this level for the RDS task. The clearest deficits emerged at 60% correlation: only 9% of NC subjects performed below the cut-off, whereas 67% of RT subjects and 39% of LT subjects were impaired by this criterion ($\chi^2 = 15.82$, $P = 0.0004$). The result at 50% correlation was similar: 17% of NC subjects performed below the cut-off, compared with 43% and 39% for the RT and LT groups, respectively, but in this case these differences failed to reach statistical significance ($\chi^2 = 3.86$, $P = 0.15$).

Subsidiary analysis

Several subsidiary analyses were carried out in order to examine the possible contribution of extraneous variables to the results obtained. First, comparing the two temporal lobe groups for Full Scale IQ, a slight difference was found favouring the LT group ($F(1,29) = 4.38$, $P = 0.045$). This effect cannot explain the results on the stereoscopic task, since an analysis of covariance using IQ as the covariate and performance on global stereopsis as the dependent variable did not show any effect of the covariate ($F(1,28) = 0.18$).

The next analysis assessed the effect of removal size on performance. Comparing size of removal along the first and along the third temporal gyri in the two patient groups, we found a significant difference ($F(1,29) = 6.50$, $P < 0.01$), reflecting the typically larger removals in the right cerebral hemisphere. In order to determine whether this variable could account for the slightly worse performance seen after RT removal on the global stereopsis task, we submitted the data from that task to further analyses of covariance, using removal size as the covariate. Neither removal extent along the first or third temporal gyrus resulted in a significant covariate ($F(1,28) = 0.27$; $F(1,28) = 1.84$, $P = 0.18$). Finally, in order to evaluate the possible effect of visual field deficits among those subjects who had had perimetric testing, we divided the subjects into two subgroups, with and without a partial upper quadrantanopia. A three-way analysis of variance was carried out with Lesion Side and Visual Field Deficit as between-subject variables and Binocular Correlation as the within-subject variable. There were no significant effects or interactions of the visual field factor ($F<1$ in all cases), demonstrating that this variable did not exert a measurable influence on global stereopsis.

DISCUSSION

This study has shown that local stereoacuity remains intact and that performance on a global stereoscopic task is impaired significantly after left or right temporal lobectomy. In the latter task, all subjects performed very well when the binocular correlation between the random-dot elements was high (100%, 90% and 80%). With lower binocular correlations (70%, 60% and 50%) differences between groups appeared, both temporal lobe groups performing worse than normal control subjects. As expected, all subjects were at chance at 40% binocular correlation. The impairment in global stereopsis obtained here is similar to our previous results using a different paradigm (Ptito and Zatorre, 1988).

The dissociation between local and global stereopsis was clear in the present study. There were no significant differences between groups on the local stereoscopic task, in contrast to the statistically highly significant differences observed on the RDS task. The objection might be raised that the local stereoscopic task was not sufficiently sensitive to subtle deficits in stereoacuity; however, when we examined only those subjects who obtained the best stereoacuity thresholds (4 s of arc), it is notable that the group differences in the RDS task remained between the temporal lobe patients and the normal control subjects. Thus even selected patients with excellent stereoacuity still have difficulty detecting the figures in the RDS. Moreover, the proportion of subjects that obtained the best threshold was very similar across groups, so that there does not appear to be any difference in the distribution of stereoacuity ability in the patient population as compared with the normal control sample.

The deficit in global stereopsis in the presence of intact local stereopsis resembles Cowey and Porter's (1979) results with monkeys that had undergone bilateral inferior temporal cortex ablations. The results do not, however, parallel those of Cowey (1985) who found a mild deficit in both local and global stereopsis in monkeys with large inferior temporal lesions. One possible explanation for this discrepancy is that the lesions in the monkeys (Cowey, 1985) were bilateral and extended posteriorly as far as the inferior occipital sulcus, whereas the lesion in our patient population involved more anterior regions of inferior temporal cortex.

Interestingly, the patients with right-sided removals performed slightly worse than those with a lesion on the left at 70% and 60% binocular correlation. These data are concordant with findings using normal subjects who show a left visual field superiority in treating binocular depth information (Durnford and Kimura, 1971; Grabowska, 1983). The results are also in agreement with those of several authors who report that patients with right hemisphere lesions exhibit marked deficits in global stereopsis (Carmon and Bechtoldt, 1969; Benton and Hécaen, 1970; Hamsher, 1978).

An important point to consider in interpreting these results is the possibility that the difference between the effects of right and left-sided removals is due to the well-known visual perceptual impairment associated with damage to the right temporal and posterior neocortex (Milner, 1990) as opposed to an asymmetry in global stereoscopic processing. In the present experiment, subjects with right temporal lesions may have had difficulty discriminating form from texture in the degraded figures with low binocular correspondence, which may account for their poorer performance. This factor, however, could not account for the global stereoscopic disturbance of the left temporal group, as there is no evidence that damage to the left temporal lobe causes a visual-perceptual deficit. In any case, our task did not require any explicit judgement of form, that is, the subjects did not have to identify the form but simply indicate whether the clusters of elements having the same depth plane were in front of or behind the screen.

Before discussing the possible mechanisms involved in local and global stereopsis, several factors that may have contributed to the results should be discussed. First, Lehmann and Wälchli (1975) attributed the cause of impaired stereopsis to generalized cognitive impairment rather than to localized brain lesions. This hypothesis cannot explain the results obtained here, as we selected only subjects with IQ ratings above 75 and this factor was found not to correlate with performance on the task. In addition, the task was obviously well understood since almost all the subjects obtained perfect scores when the RDS with high binocular correlations were used.

A second factor that may have interfered with performance is the presence of a visual field defect. We were able to obtain formal perimetric test results on a sufficient number of cases to carry out reliable statistical analyses, and no effect of visual field loss on either local or global stereopsis was found, in agreement with the reports of several authors (e.g., Danta *et al.*, 1978; Ross, 1983; Ptito and Zatorre, 1988).

A third factor that may have contributed to the greater impairment of performance in the right temporal lobe group on global stereopsis is lesion extent along the sylvian fissure and inferotemporal neocortex. Our statistical analysis showed, however, that lesion size could not account for the observed group differences, suggesting that the right temporal lobe group's worse performance is not directly related to their slightly more extensive resections.

Notwithstanding lesion side, the fact that local stereoscopic thresholds, studied independently of global stereopsis, were found to be unaffected by excision of anterior temporal neocortex fits the notion of functional streams of processing in the visual system. Within the context of local and global stereopsis as measured here, we would expect closely related but not identical areas in the brain to represent these two aspects of stereopsis, consistent with the view that there is a hierarchical organization of the visual pathways originating in the striate cortex leading into temporal cortex (*see* Desimone and Ungerleider, 1989, for a review). Cowey and Porter's (1979) and Cowey's (1985) results in the monkey, together with the data obtained here, suggest that global stereopsis is mediated in temporal lobe areas that receive information about local disparities from more posterior areas. Several studies, both anatomical and physiological, support this contention. Anatomically, the temporal lobe receives visual information that has been through at least two stages of visual processing (Cowey and Porter, 1979), suggesting that this area must have an integrative role in higher-order visual processing such as global stereopsis. Poggio and Poggio (1984) reported that a majority of neurons in areas 17 and 18 of the macaque cortex are sensitive to horizontal retinal disparity, which indicates that there exist in the visual cortex of the monkey mechanisms for 'local' stereopsis appropriate for detecting unambiguous disparities. These neurophysiological findings also provide evidence that neurons of the primary visual cortex of the monkey are capable of signalling the relative positions of objects separated in depth, and suggest that sensitivity to global stereopsis cues increases as the hierarchy of visual areas is ascended (Poggio *et al.*, 1988) towards IT cortex. In fact, Gross *et al.* (1981) have reported that almost every receptive field of IT neurons includes the fovea, and that the receptive fields of more than half these units extend well into the ipsilateral visual field, suggesting that the temporal lobes may be responsible for relating disparity information from both halves of the visual field. Finally, Gross *et al.* (1981) also found that the receptive fields of IT neurons are very large, their median size being about 25°.

The characteristics described above make it likely that IT units would be maximally excited by the multiple disparities produced across a wide area of the retina by, for example, RDS (Cowey and Porter, 1979). The association of IT neurons with global stereopsis lends support to the existence of a hierarchical model whereby IT neurons obtain their input from striate cortex via several synapses involving other visual areas where local disparity may be initially coded. Such a model is also consistent with Bishop's (1981) view that 'only local neural circuits need be involved in local stereopsis whereas the further stages of neural processing must involve larger-scale cooperative interactions between these local neural elements' (p. 443). Our results with human subjects give additional support to this position since temporal lobectomy, particularly if it involves the right cerebral hemisphere, impairs global stereopsis but leaves local stereopsis intact.

The deficit in global stereopsis was consistently observed, but it was not severe, probably due to the unilateral nature of our patient group's lesions. We would predict that bilateral IT cortex lesions would entail greater difficulties with global stereopsis. This deficit, however, would still be separable from the subject's ability to process the elementary dimensions of visual stimuli in order to carry out local stereopsis.

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REFERENCES

BENTON AL, HÉCAEN H (1970) Stereoscopic vision in patients with unilateral cerebral disease. *Neurology, Minneapolis*, **20**, 1084–1088.

BISHOP PO (1981) Neural mechanisms for binocular depth discrimination. In: *Advances in Physiological Sciences*. Volume 16, *Sensory Functions*. Edited by E. Grastyán and P. Molnár. Oxford: Pergamon Press, and Budapest: Akadémiai Kiadó, pp. 441–449.

CARMON A, BECHTOLDT HP (1969) Dominance of the right cerebral hemisphere for stereopsis. *Neuropsychologia*, **7**, 29–39.

COOPER J, WARSHOWSKY J (1977) Lateral displacement as a response cue in the Titmus Stereo Test. *American Journal of Optometry and Physiological Optics*, **54**, 537–541.

COOPER J, FELDMAN J (1979) Assessing the Frisby Stereo Test under monocular viewing conditions. *Journal of the American Optometric Association*, **50**, 807–809.

COWEY A (1985) Disturbance of stereopsis by brain damage. In: *Brain Mechanisms and Spatial Vision*. Edited by D. J. Ingle, M. Jeannerod and D. N. Lee. Dordrecht. Boston: Nijhoff, pp. 259–278.

COWEY A, PORTER J (1979) Brain damage and global stereopsis. *Proceedings of the Royal Society of London, B*, **204**, 399–407.

DANTA G, HILTON RC, O'BOYLE DJ (1978) Hemisphere function and binocular depth perception. *Brain*, **101**, 569–589.

DESIMONE R, UNGERLEIDER LG (1989) Neural mechanisms of visual processing in monkeys. In: *Handbook of Neuropsychology*, Volume 2. Edited by F. Boller and J. Grafman. Amsterdam: Elsevier, pp. 267–299.

DURNFORD M, KIMURA D (1971) Right hemisphere specialization for depth perception reflected in visual field differences. *Nature, London*, **231**, 394–395.

FRISBY JP (1980) The Frisby Stereotest: amended instructions. *British Orthoptic Journal*, Number **37**, 108–112.

GRABOWSKA A (1983) Lateral differences in the detection of stereoscopic depth. *Neuropsychologia*, **21**, 249–257.

GROSS CG, BRUCE CJ, DESIMONE R, FLEMING J, GATTASS R (1981) Cortical visual areas of the temporal lobe: three areas in the macaque. In: *Cortical Sensory Organization*. Volume 2, *Multiple Visual Areas*. Edited by C. N. Woolsey. Clifton, NJ: Humana Press, pp. 187–216.

HAMSHER K DE S (1978) Stereopsis and unilateral brain disease. *Investigative Ophthalmology and Visual Science*, **17**, 336–343.

Holmes G, Horrax G (1919) Disturbances of spatial orientation and visual attention, with loss of stereoscopic vision. *Archives of Neurology and Psychiatry, Chicago*, **1**, 385–407.

Howard HJ (1919) A test for the judgment of distance. *American Journal of Ophthalmology*, **2**, 656–675.

Julesz B (1971) Foundations of Cyclopean perception. Chicago and London: University of Chicago Press, pp. 361–365.

Julesz B (1978) Global stereopsis: cooperative phenomena in stereoscopic depth perception. *Handbook of Sensory Physiology*. Volume 8, *Perception*. Edited by R. Held, H. W. Leibowitz and H.-L. Teuber. Berlin: Springer.

Larson WL (1987) Does a small field of view degrade stereoacuity? *American Journal of Optometry and Physiological Optics*, **64**, 110–113.

Larson WL (1990) An investigation of the difference in stereoacuity between crossed and uncrossed disparities using Frisby and TNO tests. *Optometry and Vision Science*, **67**, 157–161.

Larson WL, Lachance A (1983) Stereoscopic acuity with induced refractive errors. *American Journal of Optometry and Physiological Optics*, **60**, 509–513.

Lehmann D, Wälchli P (1975) Depth perception and location of brain lesions. *Journal of Neurology*, **209**, 157–164.

Milner B (1990) Right temporal-lobe contribution to visual perception and visual memory. In: *Vision, Memory, and the Temporal-Lobe*. New York: Elsevier, pp. 43–53.

Poggio GF, Poggio T (1984) The analysis of stereopsis. *Annual Review of Neuroscience*, **7**, 379–412.

Poggio GF, Gonzalez F, Krause F (1988) Stereoscopic mechanisms in monkey visual cortex: binocular correlation and disparity selectivity. *Journal of Neuroscience*, **8**, 4531–4550.

Ptito A, Zatorre RJ (1988) Impaired stereoscopic detection thresholds after left or right temporal lobectomy. *Neuropsychologia*, **26**, 547–554.

Riddoch G (1917) Dissociation of visual perceptions due to occipital injuries, with especial reference to appreciation of movement. *Brain*, **40**, 15–57.

Ross JE (1983) Disturbance of stereoscopic vision in patients with unilateral stroke. *Behavioural Brain Research*, **7**, 99–112.

Rothstein TB, Sacks JG (1972) Defective stereopsis in lesions of the parietal lobe. *American Journal of Ophthalmology*, **73**, 281–284.

Sasieni LS (1978) The Frisby stereotest. *Optician*, **176**, No. 4544, 7–10.

Walraven J (1975) Amblyopia screening with random-dot stereograms. *American Journal of Ophthalmology*, **80**, 893–900.

Westheimer G, McKee SP (1980) Stereogram design for testing local stereopsis. *Investigative Ophthalmology and Visual Science*, **19**, 802–809.

Winer BJ (1971) *Statistical Principals in Experimental Designs*. Second edition New York: McGraw-Hill.

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NEUROLOGICAL DISEASE IN XERODERMA PIGMENTOSUM

DOCUMENTATION OF A LATE ONSET TYPE OF THE JUVENILE ONSET FORM

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SUMMARY

Xeroderma pigmentosum (XP) is an autosomal recessive, neurocutaneous disorder characterized by sunlight-induced skin cancers and defective DNA repair. Many XP children develop a primary neuronal degeneration. We describe 2 unusual XP patients who had a delayed onset of XP neurological disease. Somatic cell genetic studies indicated that they have the same defective DNA repair gene and are both in XP complementation group A. These 2 patients, together with a group A patient previously reported from London, establish as a distinct clinical entity the late onset type of the juvenile onset form of XP neurological disease. The functional capacity of these patients' cultured fibroblast strains to survive after treatment with ultraviolet radiation indicates that their DNA repair defect is less severe than that of typical group A patients who have a more severe neurodegeneration with an earlier symptomatic onset. The premature death of nerve cells in XP patients (which is presumably due to their inherited defects in DNA repair mechanisms) suggests that normal repair of damaged DNA in neurons is required to maintain integrity of the human nervous system.

INTRODUCTION

Xeroderma pigmentosum (XP) was the first human neurodegenerative disease known to be due to inherited defects in the repair of DNA damaged by certain types of physical

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or chemical agents (Cleaver, 1968; Robbins *et al.*, 1974). It is an autosomal recessive inherited disease, most notable for acute sun sensitivity, pigmentation abnormalities, and malignancies on sun-exposed skin (Robbins *et al.*, 1974; Robbins, 1987*a*, 1988). These abnormalities are caused by inherited defects in mechanisms involved in the repair of DNA damaged by the harmful ultraviolet radiation (UV) in sunlight. Somatic cell genetic studies of cultured XP fibroblast strains indicate at least 9 genetic forms of the disease exist: the XP 'variant' form, which has normal rates of DNA nucleotide excision repair and the 8 forms which are defective in DNA nucleotide excision repair and comprise the XP complementation groups designated A to H (Robbins, 1988; Bootsma *et al.*, 1989). Presumably each of these 9 genetic forms of XP has a defect in a specific gene.

Some XP patients develop a progressive neurodegeneration. A large number of neurologically affected patients have been described in complementation group A (Reed *et al.*, 1965, 1969, 1977; der Kaloustian *et al.*, 1974; Robbins *et al.*, 1974, 1983; Sugita *et al.*, 1977; Andrews *et al.*, 1978; Pawsey *et al.*, 1979; Hashem *et al.*, 1980; Stefanini *et al.*, 1980; Mitoh *et al.*, 1983; Kato *et al.*, 1985; Kenyon *et al.*, 1985; Mimaki *et al.*, 1985, 1986, 1989; Origuchi *et al.*, 1987; Sato *et al.*, 1987; Tate *et al.*, 1987; Tachi *et al.*, 1988). A smaller number of patients has been described in group D (Robbins *et al.*, 1974; Thrush *et al.*, 1974; Andrews *et al.*, 1978; Robbins, 1988). These group A and group D patients establish the existence of 'XP neurological disease' as a distinct clinical entity common to at least these two complementation groups. The neurological signs and symptoms include microcephaly, cerebral dysfunction, ventricular dilatation and cerebral cortical atrophy, extrapyramidal (basal ganglia) and cerebellar disturbances, corticospinal tract abnormalities, sensorineural deafness, and a peripheral neuropathy (characterized by hyporeflexia which progresses to areflexia). Biopsy studies of peripheral nerve indicate that XP neurological disease is a primary neuronal degeneration (Thrush *et al.*, 1974; Fukuhara *et al.*, 1982; Hakamada *et al.*, 1982; Sasaki *et al.*, 1984; Röyttä and Anttinen, 1986; Origuchi *et al.*, 1987; Tate *et al.*, 1987; Tachi *et al.*, 1988). Autopsy studies confirm this interpretation (De Sanctis and Cacchione, 1932; Yano, 1950; Reed *et al.*, 1969, 1977; Hokkanen *et al.*, 1969; Lewis *et al.*, 1978; Ogawa *et al.*, 1976; Sasaki *et al.*, 1984; Röyttä and Anttinen, 1986).

It has been suggested that XP neurological disease is due to the patient's DNA repair defect (Robbins *et al.*, 1974, 1983; Andrews *et al.*, 1978; Robbins, 1983, 1988, 1989). Presumably there is a lethal accumulation of unrepaired neuronal DNA damaged not by UV (which cannot reach the nervous system) but by intraneuronal metabolites and/or physicochemical events. This DNA damage hypothesis is based primarily on the relationship between the severity of a patient's DNA repair defect and both the age of onset and the rapidity of progression of the neurodegeneration: the earlier the symptomatic onset of XP neurological disease, the more severe is the patient's inherited DNA repair defect, as measured by the survival of the patient's fibroblasts after their exposure to UV in tissue culture.

XP neurological disease has been classified according to its age of symptomatic onset (Robbins, 1989). All reported neurologically symptomatic patients have had the juvenile onset form, becoming symptomatic before 21 yrs of age. The overwhelming majority of cases with the juvenile onset form of XP neurological disease are in complementation group A (Reed *et al.*, 1965, 1969, 1977; Kleijer *et al.*, 1973; der Kaloustian *et al.*, 1974; Sugita *et al.*, 1977; Takebe *et al.*, 1977; Andrews *et al.*, 1978; Handa *et al.*, 1978; Mitoh *et al.*, 1983; Mimaki *et al.*, 1985, 1989; Tachi *et al.*, 1988; Robbins, 1988, 1989). Since their initial neurological signs (usually intellectual impairment and delayed motor development) occur before 7 yrs of age, the patients are classified as having an early onset type of the juvenile onset form. Several group D patients and 1 group G patient have been reported with an intermediate onset type, having become symptomatic between ages 7 and 12 yrs (Robbins *et al.*, 1974; Thrush *et al.*, 1974; Andrews *et al.*, 1978; Cheesbrough, 1978; Keijzer *et al.*, 1979). The existence of a late onset type of the juvenile onset form was raised as a possibility when we reported that a group A patient, XP12BE (the 12th XP patient studied in Bethesda (BE)), had not become symptomatic until her teens (Robbins *et al.*, 1983; Robbins, 1988). Subsequently, a second group A patient, Case 2 of Kenyon *et al.* (1985), was reported in London (LO) to have been asymptomatic until 20 yrs of age. We designated this patient as XP1LO (Kraemer *et al.*, 1975; Andrews *et al.*, 1978), in accordance with the standardization of nomenclature (Kleijer *et al.*, 1973) now widely used for XP patients and their cell strains. This patient had previously been designated as 'Gillian T' by Koller (1948) (personal communication, P. Rudge), as 'an 8-yr-old girl' by Smithers and Wood (1952), and as 'XP-1 of London' by Parrington *et al.* (1971), Baden *et al.* (1972) and Robbins *et al.* (1974).

We now present the clinical history of a new patient, XP19BE, who had symptomatic onset of XP neurological disease in his teens. We also present DNA repair studies on his cultured fibroblasts which show that he is in XP complementation group A, that the level of his DNA nucleotide excision repair is unusual for a group A patient, and that the ability of his UV-treated fibroblasts to survive is in the range given for the cells from the other 2 late onset type patients, XP12BE and XP1LO. We also present the first complete detailed clinical history of patient XP12BE, review the neurological abnormalities of patient XP1LO, and compare the clinical severity of disease in these 3 group A patients. We conclude that these 3 patients represent, and thereby establish, a late onset type of the juvenile onset form of XP neurological disease and that their neurodegeneration is probably caused by DNA repair defects which are milder than those of patients with the early onset type. Abstracts of some of the findings have been published (Robbins, 1987*b*; Robbins *et al.*, 1987).

METHODS

Growth reference parameters

Standard deviations for our patients' weight, height, and head circumference were calculated by Susan R. Rose (personal communication) based on data published by Hamill *et al.* (1977).

Cell cultures

Except for the strain from patient XP19BE, the skin fibroblast strains were obtained from the American Type Culture Collection, Rockville, MD. The cell strain from patient XP19BE was obtained from the NIGMS Human Genetic Mutant Cell Repository located at the Coriell Institute for Medical Research, Camden, NJ, where it is listed as a group A strain and designated as GM 1630 (formerly designated XP1WI). Stock cultures were grown as described previously (Barrett *et al.*, 1981). Tests for mycoplasma infection of the strains were routinely negative.

Autoradiography and complementation group assignment

UV-induced unscheduled DNA synthesis (UDS) of the fibroblast strain from patient XP19BE was determined by autoradiography quantifying the uptake of tritiated thymidine into the DNA of UV-irradiated cells during the first 3 h of DNA repair. Such UV-induced UDS is a manifestation of DNA nucleotide excision repair. XP complementation group assignment was accomplished by determining whether or not fusing the XP19BE cells to reference XP cells resulted in normalization of the patient's defective rates of UV-induced UDS. The techniques have been described in detail previously (Kraemer *et al.*, 1975; Petinga *et al.*, 1977).

Cell survival determination

The ability of the fibroblast strain from patient XP19BE to survive after irradiation with 254 nm UV was determined by the colony-forming ability assay described previously (Andrews *et al.*, 1978; Barrett *et al.*, 1981). The assay depends on the ability of the irradiated cells to divide and form colonies (aggregates of 30 or more cells) within 2–3 wks. From the data obtained in the 8 replicate experiments performed, survival parameters and a survival curve were calculated by the method of Tarone *et al.* (1983). The post-UV survival curves of the 10 normal strains, the 5 early onset type group A strains, the 2 late onset type group A strains (XP12BE and XP1LO), and the XP8LO group A strain were recalculated by the method of Tarone *et al.* (1983) from data reported previously (Andrews *et al.*, 1978; Barrett *et al.*, 1981). The D_0 value (J/m^2) was obtained from the exponential portion of each survival curve and represents the UV dose required to reduce the colony-forming ability from any point on that portion of the curve to 37% (1/e) of that point. Thus comparisons of D_0 values are equivalent to comparisons of slopes of the exponential portion of the survival curves.

CASE REPORTS

Case 1 (XP12BE)

The twelfth patient of our National Institutes of Health (NIH), Bethesda (BE), XP patient series (XP12BE) is a 22-yr-old white woman (born February 2, 1965) who was the product of a pregnancy in a gravida 3, para 1, 27-yr-old woman whose second pregnancy had been electively aborted following a first trimester rubella infection. At 6 wks past the expected date of confinement, an unsuccessful attempt to induce labour was followed by a caesarean section. Her birth weight was 3.8 kg (+1.2 SD), length 50.8 cm (+0.5 SD), and head circumference 34.3 cm (±0 SD). Her early developmental milestones were normal, with sitting at 5–6 months, walking at 10 months, speaking a few words at 12 months and phrases by 18 months, being toilet trained at 2 1/12 yrs, and riding a tricycle at 2 yrs and a bicycle at 5–6 yrs.

At age 3 months she suffered an acute sun-sensitivity reaction the first time she went outdoors, in early May, near Charleston, West Virginia. Just after noon she had been placed for approximately 1 h in a playpen which was almost entirely covered by a sheet to protect her from the wind. Despite apparently being only exposed to indirect sunlight, by evening she had developed significant erythema on exposed skin and by the next day these exposed areas were swollen (no blistering was noted). Following this exaggerated reaction, she was always fully covered when taken outdoors. Nonetheless, 1 month later her right arm accidentally became exposed to noon sunlight for a few minutes and by evening had considerable erythema and pinpoint blistering which worsened the next day as the arm became swollen. Thereafter, despite attempts to protect her from sunlight, she continued to have erythema and swelling after only minimal sunlight exposure. Freckles developed on sun-exposed skin before the age of 4 yrs, and the diagnosis of XP was made by a dermatologist when she was 4 3/12 yrs of age. She received topical 5-fluorouracil treatment to areas of skin containing actinic keratoses and had individual lesions treated with cryotherapy. When first assessed at the Dermatology Branch, NIH, at age 4 9/12 yrs, the skin over the face, neck, and dorsa of the arms and hands was noted to be extremely dry and rough in texture with multiple light brown freckles 2–4 mm in diameter.

At the age of 7 8/12 yrs, she received the first of several more complete evaluations at the NIH. Her weight was 19.9 kg (−0.9 SD), height 118 cm (−1.1 SD), and head circumference 49.5 cm (−1.5 SD). Sun-exposed areas of skin were dry and showed freckling, the latter most marked on the head and neck. She had had 2 skin neoplasms by this time. General physical examination was unremarkable. Her bone age was approximately 6 yrs by the standards of Greulich and Pyle (1959); spine radiographs showed osteoporosis. Psychometric testing revealed a Slosson Intelligence Test IQ of 96 and a Vineland Social Maturity Scale age equivalent score of 7 10/12 yrs. An EEG was abnormal during drowsiness and light sleep with paroxysmal slow wave or spike-and-wave bursts.

At the age of 7 10/12 yrs, on neurological examination she was alert and orientated. Cranial nerve function was normal. Muscle tone and strength were normal, but she had slight clumsiness, more on the left than the right. Her walking was normal, except that in tandem walking she tended occasionally to fall to either side. She had some difficulty with rhythmic rapid alternating movements, and in the finger-nose test, and heel-knee-shin tests bilaterally. Tendon reflexes could not be elicited even with reinforcement. Plantar stimulation produced only withdrawal. On sensory testing, there appeared to be some reduction in light touch sensation below the knees; other modalities were intact. Motor nerve conduction velocity (MNCV) in the right ulnar nerve was 49 $m \cdot s^{-1}$ and 50 $m \cdot s^{-1}$ in the right peroneal nerve. Needle electromyography (EMG) of the right quadriceps was normal. At 8 0/12 yrs of age, an audiogram showed a bilateral hearing loss of 35 and 40 dB at 8000 Hz. At age 8 6/12 yrs, she had her first pathologically documented skin malignancy removed, a sclerosing basal cell carcinoma of the cheek.

Multiple school evaluations had been performed because of concern about learning difficulties. In first grade at the age of 6 7/12 yrs, she scored in the 42 centile on the Metropolitan Readiness Test and in grade 3.7 obtained a composite battery grade equivalency score on the Education Development Series of 3.2. At the age of 10 4/12 yrs, in grade 4.9, she had Peabody Individual Achievement Test (PIAT) grade equivalent scores in Mathematics 2.5, Reading Recognition 5.2, Reading Comprehension 4.2, Spelling 4.4, and General Information 3.5. However, 3 months later, in grade 5.1, she scored on the Metropolitan Achievement Test grade equivalent scores in Word Knowledge of 4.2, Word Discrimination 4.9, Reading 4.2, Spelling 4.7, and Arithmetic 3.2.

At the age of 10 8/12 yrs, her weight was 24.5 kg (−1.4 SD), height 130 cm (−1.8 SD), and head circumference 49.5 cm (−2.0 SD). She remained freckled on sun-exposed areas of skin (for photograph, *see* Robbins, 1988). On neurological examination, she was alert and cooperative and had no language disorder. Cranial nerve function was grossly normal. Her muscle bulk was small, but strength and tone were normal for the generally reduced muscle bulk. She had no tremor and performed rhythmic rapid alternating movements well. Her gait was normal including tandem walking. Tendon reflexes could not be elicited in either the upper or lower limbs. Formal sensory testing revealed no abnormality. Menarche occurred at 13 1/12 yrs and was followed by regular menstrual periods. At the age of 13 4/12 yrs, an audiogram (fig. 1) showed progression of the sensorineural hearing loss, involving both 8000 Hz and 4000 Hz. Speech reception threshold was 5 dB with 100% discrimination in both ears.

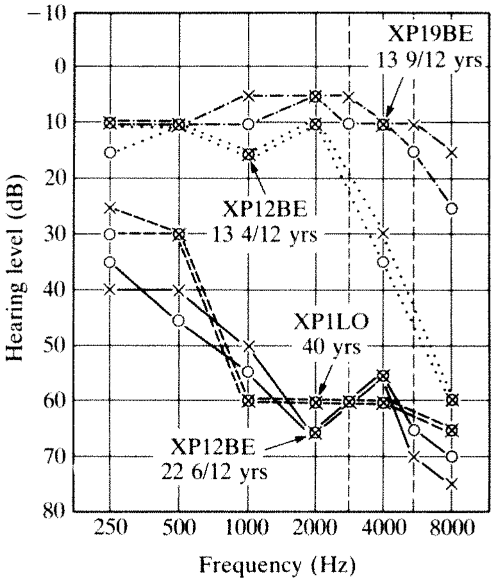

FIG. 1. Pure tone audiograms obtained from *Case 1* (XP12BE) and *Case 2* (XP19BE) from present study and from *Case 2* (XP1LO) of Kenyon *et al.* (1985). The upper set shows that the hearing loss of XP19BE was less, when he was 13 9/12 yrs of age, than the loss in XP12BE when she was younger (age 13 4/12 yrs). The lower set of audiograms shows that the hearing loss of XP12BE, when she was 22 6/12 yrs of age, was already equivalent to that of XP1LO at age 40 yrs. Audiogram of XP1LO redrawn from Kenyon *et al.* (1985). Frequencies tested, but not labelled, are 3000 and 6000 Hz. Right ear (open circle); left ear (cross).

At the age of 15 2/12 yrs, she had a weight of 37.3 kg (−1.5 SD), height of 146.1 cm (−2.3 SD), and head circumference of 53 cm (−1.5 SD). At that time, detailed psychometric evaluation was performed. On the Wechsler Intelligence Scale for Children, Revised Edition (WISC-R) she had a Verbal IQ of 78, Performance IQ 84, and Full scale IQ 79 (for subtest scaled scores, *see* Appendix). On the Wide Range Achievement Test (WRAT) she had standard scores in Reading 100, Spelling 97, Arithmetic 72. On the Gates-MacGinitie Reading Comprehension Subtest she scored a grade equivalent of 4.5.

At the age of 16 10/12 yrs, she had a weight of 38.6 kg (−2.6 SD), height of 144.8 cm (−2.9 SD), and head circumference of 52 cm (−2.0 SD). Neurological examination revealed her to be alert and orientated. She had no language disorder, and her immediate memory was good. However, she had difficulty following complex (three-step) commands. Cranial nerves were grossly normal. Muscle strength and tone were normal, but she was slightly clumsy in fine motor movements in the upper limbs. She had no tremor on heel-knee-shin or finger-nose tests, but rhythmic rapid alternating movements in the upper limbs were slightly incoordinated. Her gait was normal except for some impairment in tandem gait. Romberg's test was negative, although on formal sensory testing there was apparently slight reduction in vibration sense distally in the lower limbs. Other sensory modalities appeared normal. Tendon reflexes could not be elicited either in the upper or lower limbs. She had bilateral extensor plantar responses. Pattern shift visual evoked responses were normal. At the age of 16 10/12 yrs, an audiogram showed progression of the hearing loss. Speech reception threshold was 25 dB with 100% discrimination in both ears.

She subsequently had detailed psychometric testing on two occasions, 4 months apart. At the age of 17 4/12 yrs on the WISC-R she had a Verbal IQ of 77, Performance IQ 78, and Full Scale IQ of 76 (for subtest scaled scores, *see* Appendix). Her WRAT standard scores were Reading 105, Spelling 99, and Arithmetic 79. At the age of 17 8/12 yrs, she had a Wechsler Adult Intelligence Scale, Revised Edition (WAIS-R) Verbal IQ of 78, Performance IQ 72, Full Scale IQ 74 (for subtest scaled scores, *see* Appendix). Her WRAT standard scores were Reading 102, Spelling 96, Arithmetic 75. Pattern shift visual evoked responses were normal. At 18 5/12 yrs of age, an audiogram showed that the hearing loss had progressed and now involved virtually all frequencies tested. Speech discrimination score was 96% at 70 dB in the right ear and 88% at 65 dB in the left.

Over the next few months, her mother felt the patient had been tripping more frequently and seemed to be more 'out of touch' and inattentive. Neurological examination at the age of 19 3/12 yrs showed her to be alert and orientated but with some clinically apparent difficulty with recent memory, calculation problems, and following simple three-step instructions. Her cranial nerve examination was normal other than the hearing loss. Fine motor control was poor bilaterally. She had difficulty walking on her heels and fell with attempts at tandem walking. There was an apparent reduction in vibration sensibility in the feet bilaterally. Tendon reflexes could not be elicited, and she had bilateral extensor plantar responses.

Following that evaluation, she was entered into a protocol at age 19 4/12 yrs to test whether isotretinoin (Accutane, 13-cis-retinoic acid) could prevent development of new skin cancers. Until then she had continued to develop skin cancers on sun-exposed, but not on unexposed skin (for colour photographs, *see* Robbins, 1988). From the age of 11 4/12 − 19 4/12 yrs of age she had accumulated at least 97 basal cell carcinomas, 1 squamous cell carcinoma, and numerous actinic keratoses. She received isotretinoin (2 mg/kg/day) from ages 19 4/12 to 21 4/12 yrs. Isotretinoin (0.5 mg/kg/day) was restarted age 22 4/12 yrs. Results of this protocol have been presented elsewhere (Kraemer *et al.*, 1988). She graduated from high school and finished an 8 month vocational rehabilitation nurse's aid training course in which she achieved an 82% overall grade. However, she began to experience greater difficulties in maintaining her balance, falling on several occasions.

A CT scan at age 20 8/12 yrs showed enlarged ventricles and prominent sulci especially in the sylvian fissure (fig. 2A). At the age of 20 11/12 yrs, on neurological examination she was alert and orientated, but her fund of knowledge was noted to be limited, she was unable to abstract propositions or provide judgements regarding common life situations, and could not perform simple arithmetical calculations. Cranial nerve function was normal except for continuing progressive hearing loss and abnormal (dysmetric) saccadic eye movements. Muscle strength and tone were appropriate for her small muscle bulk. She had slight ataxia on heel-knee-shin testing and was clumsy in rhythmic rapid alternating movements. Sensory testing revealed apparently diminished vibration sense in her feet; other modalities were intact.

At the age of 21 1/12 yrs, truncal ataxia was more prominent on a repeat neurological examination. An EEG (fig. 3A) showed a mildly slow background, intermittent brief bursts (up to 2 s) of moderate to high voltage 3–5 Hz sharp waves, and spikes bilaterally with frontal and sometimes right-sided predominance.

At the age of 21 8/12 yrs, a thorough reevaluation including a formal examination for subtle neurological signs was performed (Denckla, 1985). She showed a right hand, right foot and right eye preference. She had facial asymmetry on the left (secondary to surgery) and was unable to wink her right eye. She had a denasal voice quality with nasal aspiration and loss of pressure on plosives such as 'p', 'b', 'm'. She could sustain phonation for only 9 s. She was unable to isolate motion in upper or lower lips, and her lips were mildly weak when attempting to maintain closure. Her tongue movement was incoordinated when attempting a series of protrusion-retraction manoeuvres and was slightly weak at the tip particularly on the left. She had moderate impairment of the ability to execute a series of oral motions or repeat syllables.

Neuro-ophthalmological examination revealed abnormalities confined to the ocular movements. Corrected visual acuity was 20/20, Goldmann visual fields were full, and colour vision was normal. Pupillary responses were normal. Slit lamp evaluation of the cornea and funduscopic examination were unremarkable. Eye movements were evaluated both clinically and by eye movement recordings (with the magnetic field-scleral coil technique). The patient was orthophoric with normal stereo vision. The range of eye movements was full. Fixation was within normal limits with only a few square wave jerks noted. Optokinetic responses and vestibulo-ocular reflexes were normal. Both horizontal and vertical saccades were of normal velocity but had a tendency to fall slightly short of the target (fig. 4). Pursuit eye movements were abnormal in both horizontal and vertical directions with a low gain, requiring multiple catch-up saccades. A similar abnormality was seen when the patient attempted to suppress the vestibulo-ocular reflex by following a target moving together with her head. The difficulty with pursuit is demonstrated in fig. 4, where the eye position poorly follows a slowly moving horizontal target.

The biceps, brachioradialis, and finger jerks were depressed and the triceps, knee and ankle jerks absent bilaterally. The plantar response was flexor on the right side and equivocal on the left. Sensory testing revealed apparently reduced position sensation at the toes on the left, but normal on the right side.

Psychometric testing revealed a Wechsler Adult Intelligence Scale, Revised Edition (WAIS-R) Verbal IQ of 79, Performance IQ 77, and Full Scale IQ 76 (for subtest scaled scores, *see* Appendix). On the Wide Range Achievement Test, Revised Edition (WRAT-R), she had standard scores in Arithmetic 72, Reading 89 and Spelling 88. MNCV in the left median nerve was reduced (43 $m \cdot s^{-1}$) but the evoked muscle action potential (MAP) amplitude was normal (11.5 mV); sensory nerve conduction velocity (SNCV) in the left median nerve was also reduced (43 $m \cdot s^{-1}$) as was the amplitude of the finger/wrist sensory action potential (3.7 μV). The left peroneal MNCV was slightly reduced at 36 $m \cdot s^{-1}$; the MAP amplitude in extensor digitorum brevis was borderline (2.0 mV). H reflexes and sural sensory nerve action potentials could not be obtained on either side.

During a reevaluation at the age of 22 yrs, the mother reported that the patient did not complain about any pain with recent liquid nitrogen application to skin lesions on her hands, but she did when the liquid nitrogen was applied to similar lesions on her face. Her head circumference was 51.2 cm (−2.5 SD). Although cooperative and orientated, she was immature and child-like in her behaviour during the examination. She had dysmetric ocular saccades, restricted facial movements (probably secondary to the previous extensive facial surgery), and grossly diminished hearing. In her spontaneous gait, she had bilaterally diminished arm swing and, when walking on the outsides of her feet, had a tendency to hold her arms bilaterally in a flexed position with fisted thumb. Romberg's test was positive. When she held her arms extended in front of her, there was moderate degree of choreiform finger and hand movement along with a slight pronation drift of the left arm. Slight past-pointing and endpoint tremor were evident on finger-nose testing, and fine finger movements were clumsy. She had no gross ataxia, but excessive rebound was apparent. Her handgrip had a milking quality bilaterally. Tendon reflexes could not be elicited in the upper limbs or at the knees, but sluggish ankle reflexes were present. Muscle tone was probably normal. The plantar responses were both uncertain. Pin prick sensation in her feet was impaired.

At the age of 22 6/12 yrs, an audiogram (fig. 1) showed progressive loss of hearing. Speech discrimination score without masking was 72% at 80 dB in the right ear and 92% at 85 dB in the left ear. Right ear performance index for phonetically balanced words (PIPB) at 75, 85, 95 and 100 dB were, respectively, 56, 72, 84 and 92%. Left ear PIPB at 70, 80 and 90 dB were, respectively, 56, 68 and 88%. Brainstem auditory evoked potentials were normal, showing in the left ear interpeak latencies of I–III 2.36 ms, III–V 1.36 ms and I–V 3.72 ms, and in the right ear I–III 1.80 ms, III–V 1.80 ms and I–V 3.60 ms.

Case 2 (XP19BE)

The nineteenth XP patient in our NIH series is a 15-yr-old white boy (born October 24, 1972) who was the product of an uneventful pregnancy and breech delivery in a gravida 2, para 0 (previous hydatidiform mole), 21-yr-old woman. His birth weight was 2.3 kg (−2.0 SD), height 48.3 cm (−1.1 SD) and head circumference 30.5 cm (−1.4 SD). His early developmental milestones were normal, sitting at 8 months, crawling at about 9 1/2 months, speaking a few words at 1 yr, walking at 13 months, running at 15 months, and toilet trained at 3 yrs. His parents noted that as a toddler he seemed very clumsy, but at the age of 18 months he was able to put together small jigsaw puzzles and during early school years readily put together thousand-piece puzzles. He rode a tricycle at age 2 4/12 yrs and a bicycle at 7 3/12 yrs. He learned to play the piano at 9 yrs of age and skilfully performed the right hand parts, but had considerable difficulty with the left hand parts. During adolescence he successfully learned swimming and carpentry and participated in high school drivers' education classes.

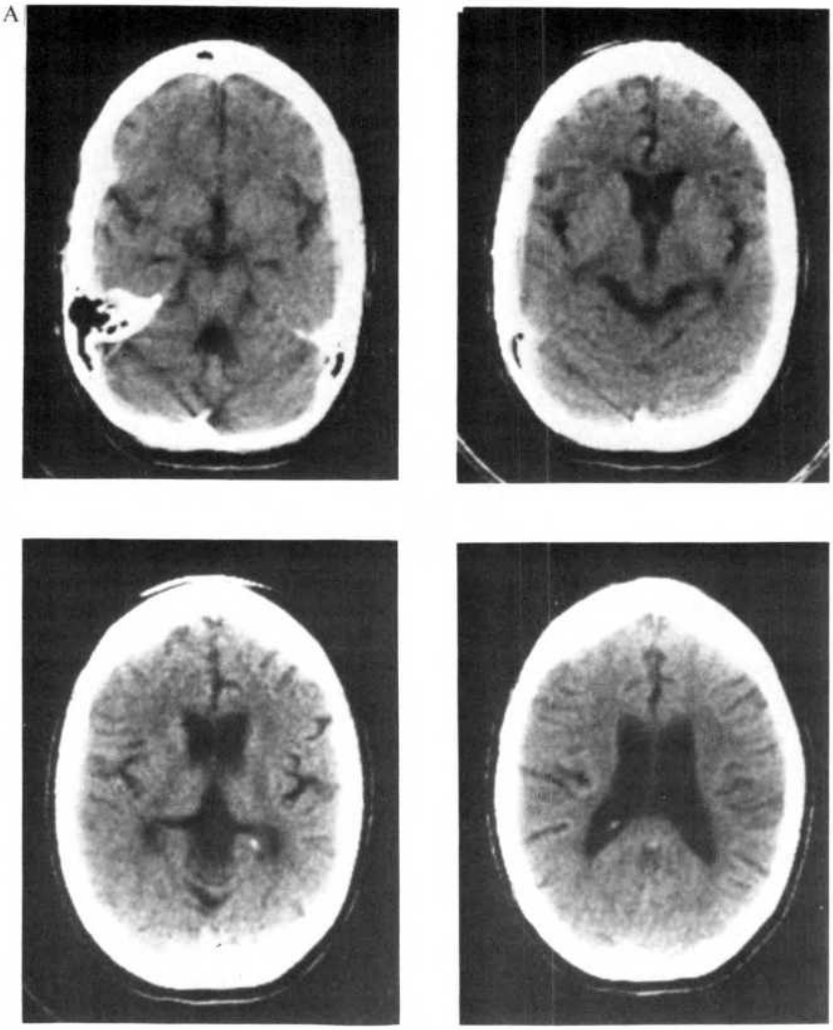

FIG. 2A.

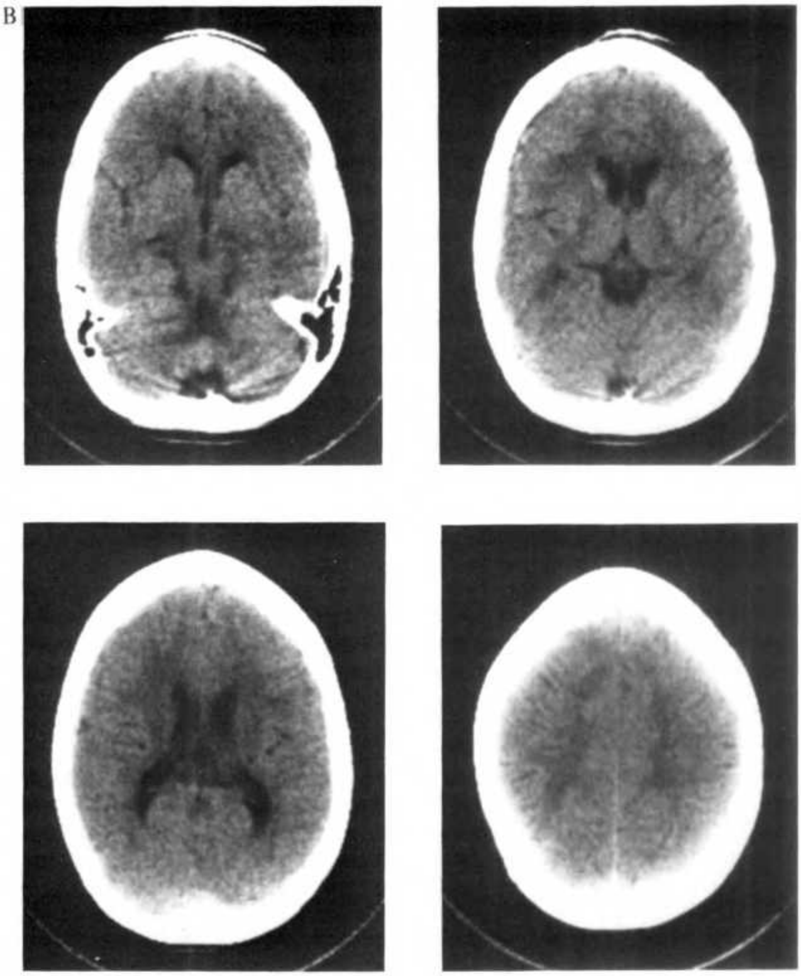

FIG. 2. CT scans for (A) *Case 1* (XP12BE) at age 20 8/12 yrs and (B) *Case 2* (XP19BE) at 14 yrs of age showing ventricular enlargement and prominent sulci.

The patient has always lived in Kansas. At the age of 3 months, while wrapped in a blanket, his face was exposed to the early afternoon January sun for approximately 15 min. About 2 h later he developed a silver-dollar-sized erythematous swelling on one cheek, which 5 h later developed a reddish-brown crust that peeled after 3−4 days. Four similar reactions occurred after 30 min sun-exposures during his fourth month of life. Suntan lotions did not prevent these acute sun-sensitivity reactions. Freckles were first noted on his face and arms at about 6 months of age. From April (6 mos of age) to June (8 mos of age), he had 4 serious sunburns after only 1 h exposures. Three to four hours after exposure to the sun, his exposed skin became pink, then red, with a marked increase in the erythema and swelling by the next morning. The swelling was so great that his eyes were visible only through tiny slits. Blisters formed on the affected skin and appeared to crust over within a few hours. His skin was maximally red when the swelling had dissipated by afternoon or evening of the second day following sun exposure (for photograph, *see* Robbins, 1988). Peeling of the crusts occurred after 3−4 days. During the entire 4-day sunburn reaction, he showed no evidence of pain or discomfort. By 1 yr of age, he had freckles on all sun-exposed areas of skin. Despite the use of topical chemical sunscreens and efforts to avoid outdoor sunlight until evening, he had several severe sunburn reactions from ages 1 to 4 yrs. Exposure to sunlight for 15 min in the summer and for 1 h in the winter was sufficient to cause these acute sun-sensitivity reactions. At 4 yrs of age, he began complaining of eye discomfort caused by sunlight and would shade or close his eyes. Since then, he has stayed outdoors only if wearing sunglasses and, when in bright sunlight, has held his hands over the rims of the glasses to provide additional shading.

At 3 4/12 yrs of age, the diagnosis of XP was made by a dermatologist. Tests of erythrocyte, urinary and faecal porphyrins were normal. At that time, he had freckling, scaling, and keratotic lesions on sun-exposed skin of the face, arms and neck. Telangiectasia and wrinkling of the skin were also present. At age 4 4/12 yrs, a histopathologically-confirmed solar (actinic) keratosis was removed from the skin of the left upper chest.

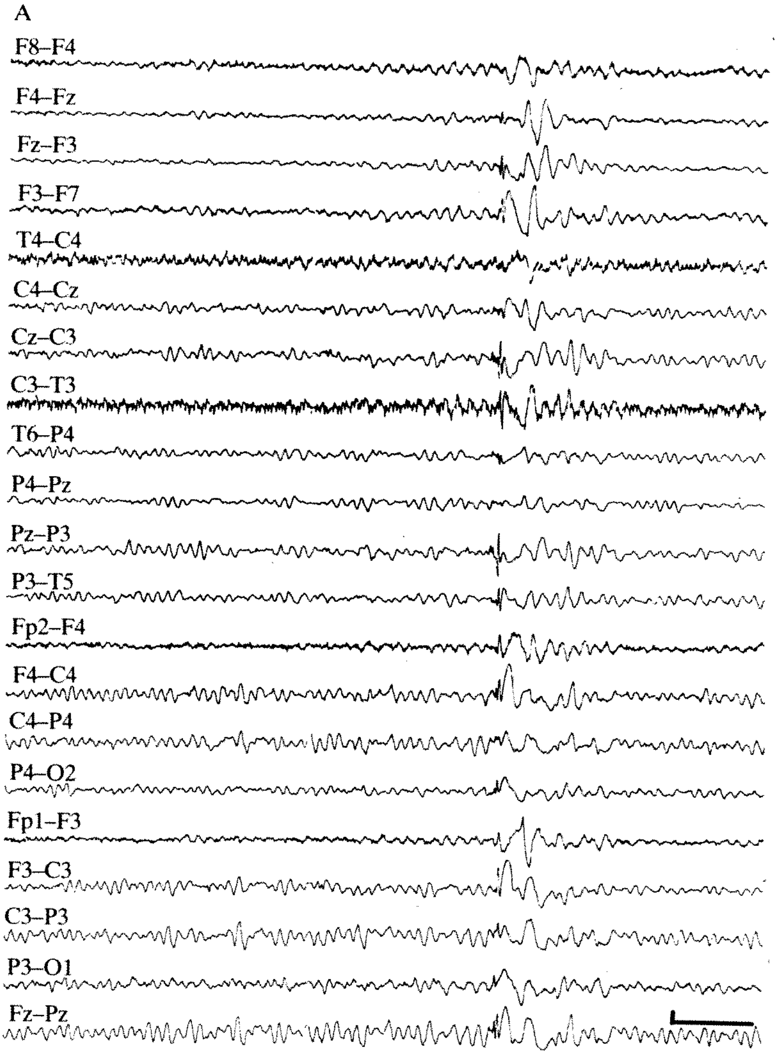

FIG. 3A.

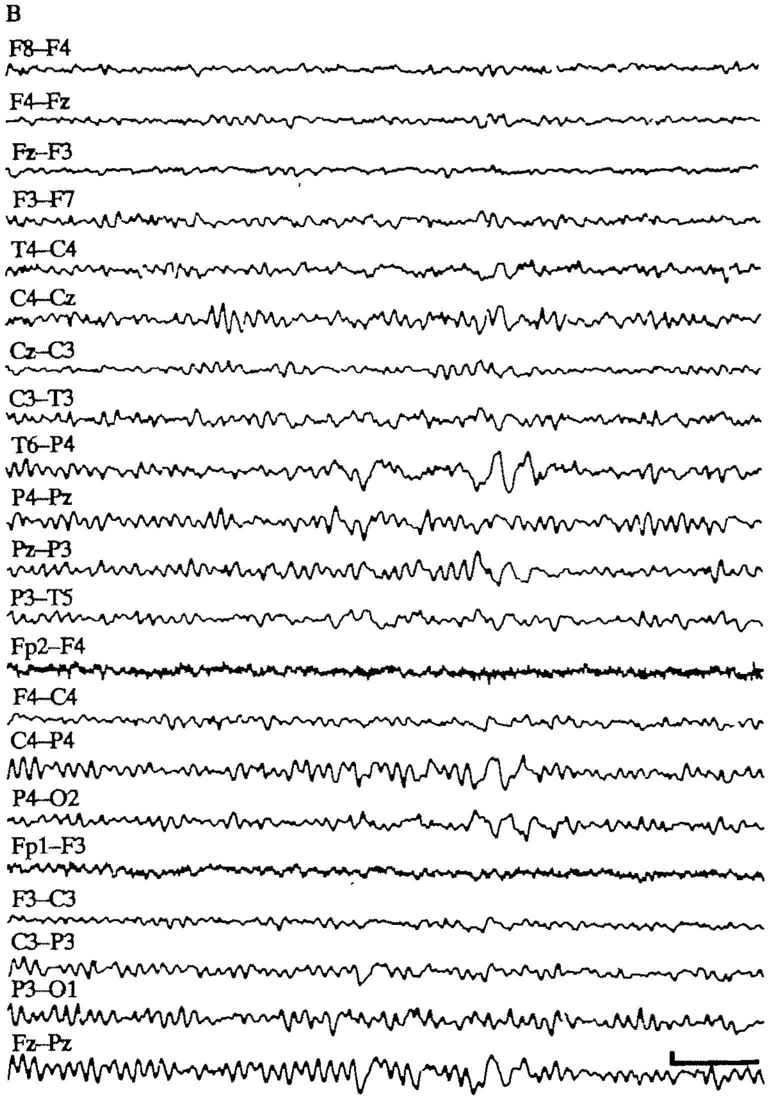

FIG. 3 EEG recordings. A, *Case 1* (XP12BE) at age 21 1/12 yrs showing a mildly slow background, intermittent brief bursts (up to 2 s) of moderate to high voltage 3–5 Hz sharp waves, and spikes bilaterally with frontal and sometimes right-sided predominance; B, *Case* 2 (XP19BE) at age 13 10/12 yrs showing a bilaterally symmetric irregular posterior rhythm of 7–8 Hz which attenuated with eye opening Calibration: 50 μV; 1 s).

At the age of 4 6/12 yrs, his weight was 13.0 kg (−2.1 SD), height 97.0 cm (−2.2 SD) and head circumference 47 cm (−2.7 SD). General physical examination was unremarkable except for his skin and feet (a moderate degree of pes planus with some genu valgum). His skin showed marked freckling which was extreme on his face and neck. Neurological examination was normal except for slight incoordination and a slightly unsteady gait. Romberg's test was negative, and reflexes were normal bilaterally. An audiogram was normal. Speech reception thresholds were 2 and 6 dB in the right and left ears, respectively.

At the age of 4 10/12 yrs, his head circumference was 48.5 cm (−1.8 SD). His skin had some new

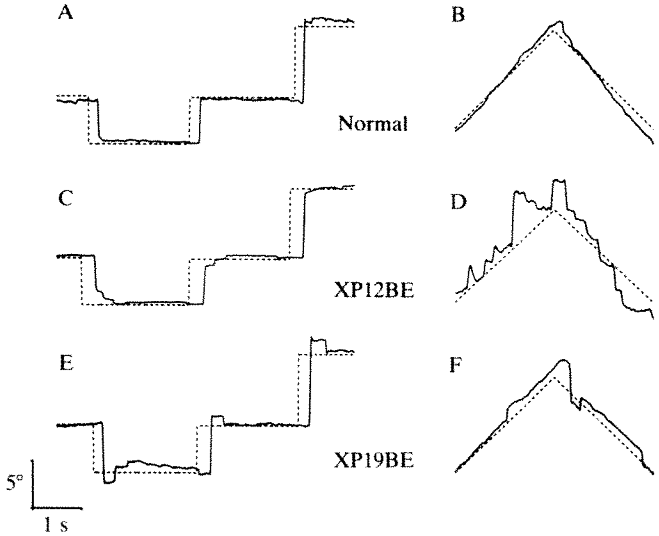

FIG. 4. Eye movement recordings. A, C, E, saccadic responses to target steps; B, D, F, horizontal smooth pursuit of a predictable target ramp moving at a constant velocity of 5 deg/s. Target position is indicated by the broken line, eye position by the solid line. Eye movements were recorded by the infrared reflection technique for the normal control and *Case 2* (XP19BE) and by the scleral search coil technique for *Case 1* (XP12BE). XP12BE shows a tendency for saccadic eye movements to fall slightly short of the target and has great difficulty in smooth pursuit; XP19BE shows hypermetria (an overshooting of saccades requiring backward corrective eye movements) and has mild abnormalities in pursuit.

crusted and slightly erythematous lesions. Those on his face and ankles were treated with topical 5-fluorouracil. Neurological examination was normal. Testing with the Wechsler Preschool and Primary Scale of Intelligence revealed a Verbal IQ of 87, Performance IQ 110, and Full Scale IQ 98 (for subtest scaled scores, *see* Appendix). On entering school, he performed average work in the first and second grades, but by third grade it became apparent that he was having learning difficulties, most severe in mathematics and reading comprehension. This was apparent in the decline in his performance on the Iowa Tests of Basic Skills which showed that his composite grade equivalent score, which was 1.5 when he was at grade level 1.8, was only 4.9 at grade level 5.8. Although his spelling and computational abilities remained at or above grade level, he did particularly poorly in reading, vocabulary, mathematical concepts and problem solving (his grade equivalent scores being more than one full grade behind his actual grade placement).

From the ages of 5 4/12 to 6 6/12 yrs of age, 3 clinically apparent actinic keratoses were treated with cryotherapy (no biopsies were obtained). At the age of 6 4/12 yrs, his weight was 16.3 kg (−1.7 SD), height 107.2 cm (−2.4 SD) and head circumference 49.2 cm (−1.6 SD). General physical examination was unremarkable. The tendon reflexes were normal, except for slightly increased knee reflexes. At 8 5/12−9 11/12 yrs of age, audiograms were normal except at 8000 Hz, where hearing levels in the right ear were 30 and 20 dB, respectively, as opposed to normal levels of 5 dB in the left ear.

At the age of 11 7/12 yrs, he received his first evaluation at the Dermatology Branch of the NIH. His weight was then 28.0 kg (−1.2 SD), height 121.9 cm (−3.4 SD) and head circumference 49.5 cm (−2.3 SD). Sun-exposed areas of skin were dry and covered with numerous hyperpigmented macules (solar lentigines, 'XP freckles') of different shades of brown (for photographs, *see* Robbins, 1988). These XP freckles occurred even on the vermillion border of his lips, which showed angular cheilitis at the corners of his mouth. Telangiectases were present on the atrophic skin of his nose. Despite the fact that he had had considerable exposure to sunlight, he was unusual for a complementation group A XP patient in that he had had only one histophathologically documented actinic keratosis and had not yet had a skin cancer. Areas of skin protected from the sun, such as the buttocks, had no freckling (for photographs, *see* Robbins, 1987*b*).

He was a pleasant and cooperative patient whose memory, orientation and language were clinically normal. His visual acuity was 20/20 in each eye. Skin of the eyelids was hyperkeratotic especially at the lash bases. The bulbar conjunctivae were injected. In the left eye, there were 6 lipoid dots in the nasal interpalpebral conjunctiva near the limbus. In the left eye, the nasal interpalpebral conjunctiva was whitened and thick in a small area near the limbus. The cornea, anterior chamber and lens were clear and the optic disc, macula and peripheral retina were normal in both eyes. Muscle strength, tone and bulk were all normal. Fine motor movements in both upper limbs were clumsy. He had a fine endpoint tremor in the upper limbs on finger-nose testing and was incoordinated in rhythmic rapid alternating movements, but his movements were accurate on heel-knee-shin testing. In walking, he tended to rotate his left foot inwards. He was somewhat unsteady in tandem walking, and this was made worse by eye closure. Sensory testing was grossly normal. The right biceps jerk and both knee jerks were reduced bilaterally, the left biceps, both triceps and both ankle jerks being only just obtainable and both brachioradialis reflexes being absent. The plantar responses were flexor; a palmomental reflex could be elicited bilaterally. At that time, entering grade 7, psychometric tests revealed a WISC-R Verbal IQ of 82, Performance IQ 91, and Full Scale IQ 85 (for subtest scaled scores, *see* Appendix). He had PIAT grade equivalent score in Mathematics 3.8, Reading Recognition 5.0, Reading Comprehension 6.2 and Spelling 4.4.

At the age of 13 9/12 yrs, an audiogram was normal except for hearing levels at 8000 Hz of 25 dB in the right ear and 15 dB in the left ear (fig. 1). Speech reception thresholds were 8 dB on the right and 5 dB on the left, and speech discrimination was 92% on the right and 100% on the left.

He was reevaluated at the age of 13 10/12 yrs, at which time his weight was 36.1 kg (−1.3 SD), height 142.2 cm (−2.3 SD), head circumference 51 cm (−2.0 SD) and blood pressure 110/75. He was alert, cooperative and orientated, with no language disturbance but his attention span seemed short. His cranial nerves were normal. Visual acuity was 20/25 bilaterally. The eyelids showed mild blepharitis. Small nasal and lateral pingueculae were present near the limbus in each eye. The cornea, anterior chamber and fundus were normal in each eye. Muscle strength, tone and bulk were normal. Fine motor movements in the upper limbs were clumsy, there was some degree of motor impersistence, and he had occasional mirror movements. He had endpoint tremor on finger-nose testing and some incoordination on repetitive rapid alternating movements. In walking, he turned his left foot inwards and was unsteady in tandem walking. Sensory testing was grossly normal. Tendon reflexes were reduced at the knees, just obtainable for the right biceps and at the ankles bilaterally, and absent for the left biceps, triceps and brachioradialis bilaterally. The plantar response was flexor bilaterally, and he had a palmomental reflex bilaterally.

At that time, entering grade 8, psychometric testing revealed a WISC-R Verbal IQ of 75, Performance IQ 92, Full Scale IQ 82 (for subset scaled scores, *see* Appendix). On the PIAT, he had grade equivalent scores for Mathematics of 5.7, Reading Recognition 5.6, Reading Comprehension 6.0 and Spelling 9.8. On the Woodcock-Johnson Psycho-Educational Battery, his reading age score was 10.2, mathematics age score 11.6, and written language age score 12.4.

On a formal examination for subtle neurological signs (Denckla, 1985) he showed an 80% right, 20% left hand preference, left foot preference, and right eye preference, consistent with a mixed (nonright) preference pattern. He had slight finger weakness in the left hand, mild truncal and extremity hypotonia, finger-nose test and heel-knee-shin test dysmetria, and amplitude variability in rhythmic rapid alternating movements. His tendon reflexes were unobtainable at the ankles bilaterally or at the right knee, were reduced at the left knee, and obtainable in the upper limbs with reinforcement. There were persistent associated overflow movements: (1) of hands when walking on the sides of the feet (more on right side); (2) jaw synkinesis; (3) overt finger movements with finger succession and initial-then-suppressed mirror movement with pronation/supination bilaterally. He failed to perform as expected for age in tandem walking backwards, balance without arms akimbo, and right-sided hopping. He was slow for age on left foot tapping, alternating heel-toe tapping, hand patting, finger tapping, and bilaterally on hand pronation–supination and finger succession.

He had dysarthria, characterized on formal evaluation, with a number of oral-motor and speech performance abnormalities. Although completely intelligible, he had improper prosadic pauses, irregular range of speech and imprecision in final consonants. The voice pitch and intensity fluctuated during conversation and with sustained vowel production. His voice was tremulous and had a denasal quality. He could sustain phonation for only 8 s. He had facial asymmetry with decreased left lower facial movement and deviation of his jaw to the right with phonation. His lips were mildly weak when attempting to maintain closure, his tongue was slightly weak on the right; reduced lip mobility was evident, more so for the upper lip. Tongue tremor was also present. Impairment of the ability to repeat syllables was moderate for labial and velar, but marked for alveolar, series. He could not sequence a series of three syllables ('p', 't', 'k') differing in place of articulation. He also had some drooling.

Nerve conduction studies were normal (left sural SNCV 47 5 $m \cdot s^{-1}$, amplitude 10.8 μV; right sural 47.9 $m \cdot s^{-1}$, amplitude 11.3 μV; right tibial MNCV 47.5 $m \cdot s^{-1}$, distal latency of 3.4 ms, MAP amplitude 7.3 mV. No H reflex was obtainable in either leg. Somatosensory evoked potentials to right median nerve stimulation had EP-N2 interpeak latency of 9.3 ms, left median EP-N2 9.8 ms, and left peroneal LP-N2 18.2 ms, all within normal limits. Brainstem auditory evoked potentials were normal, with interpeak latencies from the right ear of I–III 2.13 ms, III–V 1.73 ms and I–V 3.86 ms, and latencies of I–III 1.80 ms, III–V 1.92 ms and I–V 3.72 ms from the left. An EEG (fig. 3B) showed a bilaterally symmetric irregular posterior rhythm of 7–8 Hz which attenuated with eye opening.

He was again reassessed at the age of 14 0/12 yrs. He had slight dysmetria on ocular saccades. There was minimal weakness of facial muscles bilaterally, reduced expressive facial movements and a slight tremulousness of the tongue; otherwise the cranial nerves were normal. In his resting stance he had an increased carrying angle at the elbow for his left arm, and his left foot and leg were internally rotated. On walking he had reduced left arm swing and a slightly scissoring gait, more apparent with the left leg. Romberg's test was positive. Strength and bulk of large muscles were probably normal, but in the lower limbs he had pes cavus, hammer toes and weakness of ankle and toe extension and toe flexion. He had slight endpoint tremor on finger-nose testing, and a mild degree of rebound in both upper and lower limbs. The biceps, triceps and brachioradialis reflexes were reduced bilaterally, the knee jerks normal and the ankle jerks only just present. The abdominal reflexes were all present and the plantar responses uncertain. In sensory testing, he could not distinguish sharp from dull in his toes and distal foot bilaterally. CT scans of the head showed slightly enlarged ventricles and prominent sulci, suggesting mild diffuse atrophy (fig. 2B).

During reevaluation at age 14 4/12 yrs, neuro-opthalmological examination showed a corrected visual acuity of 20/20, full Goldmann visual fields and normal colour vision, pupillary responses, slit lamp evaluation of the cornea and funduscopy. Eye movements were assessed both clinically and by eye movement recordings (with the infrared scleral reflection technique). He was orthophoric with normal stereo vision and had a full range of eye movements. He had some fixational instability with an increase in the number of square wave jerks. Vestibulo-ocular reflexes and optokinetic responses were normal. Saccadic velocity was normal, but there was hypermetria; pursuit eye movements were only mildly abnormal, with an increase in the frequency of catch-up saccades to keep the eyes on target (*see* fig. 4).

He had a mild scoliosis to the right, pelvic obliquity with an elevated left hemipelvis, limitation of external rotation at the left hip, wasting of the intrinsic muscles of the feet and pes cavus (left greater than right). Spine radiographs confirmed the minimal thoracolumbar scoliosis to the right and showed osteoporosis and spina bifida occulta. An MRI scan of the lower thoracic and upper lumbar spine was normal.

His father, aged 42 yrs, was found to have bilateral mild pes cavus and nerve conduction evidence of a mild peripheral neuropathy of axonal type. He had a normal H reflex.

RESULTS

UV-induced unscheduled DNA synthesis (UDS) of Case 2 (XP19BE) cells

UV-induced UDS was measured by counting the autoradiographic grains over cell nuclei. The grains result from the tritiated thymidine inserted during DNA repair synthesis into stretches of DNA from which the UV-induced cyclobutane pyrimidine dimers (and possibly other photoproducts) have been excised. The mean grain counts for the 2 normal strains were 34.2 and 42.0 grains/nucleus. The reference group D (XP5BE), group C (XP9BE) and group A (XP12BE) mononuclear cells had, respectively, mean grain counts of 15.8, 5.8 and 0.7 grains/nucleus. (XP12BE cells have previously been shown to have the same minimal UV-induced UDS as typical group A strains; Petinga *et al.*, 1977.) Expressed as a percentage of the average mean grain count (38.1 grains/nucleus) of the 2 normal strains, these mean grain counts are, respectively, 41%, 15% and <2%

of normal and are similar to values obtained in prior experiments (Robbins *et al.*, 1974; Kraemer *et al.*, 1975; Petinga *et al.*, 1977). The XP19BE cells had 4.0 grains/nucleus, which is 10% of the normal value.

Complementation group assignment of Case 2 (XP19BE)

In order to determine whether an XP cell strain complements another XP strain, it is necessary to fuse the cells to form a heterokaryon cell (i.e., a multinucleate cell containing at least one nucleus from both cell strains) and then determine whether the heterokaryons have more UV-induced UDS than both of the strains when cultured separately. A mixture of XP19BE and XP12BE cells was therefore treated with killed Sendai virus to obtain cell fusion. The autoradiograms from this experiment revealed that none of the multinucleate cells had nuclei with more grains per nucleus than the nuclei in the XP19BE culture. Since some of the multinucleate cells resulting from the Sendai virus treatment of the mixture of XP19BE and XP12BE cells had to have been heterokaryons, we can conclude that the XP19BE and XP12BE cells do not complement each other and that the patients are, therefore, in the same complementation group. Thus XP19BE can be assigned to complementation group A.

In order to confirm that the XP19BE cells could complement cells from an XP patient in a different complementation group, we fused XP19BE cells with those from the group C patient XP9BE. The XP19BE and the XP9BE cells complemented each other, since we readily found clusters of nuclei in some multinucleate cells which had more UV-induced UDS than any of the nuclei in cultures of either the XP19BE cells fused to themselves or the XP9BE cells fused to themselves.

Survival of XP19BE cells after exposure to UV

The survival after UV exposure of fibroblast strains from several group A patients has been determined previously in our laboratory by assessing the ability of the cells to divide and form colonies in tissue culture (Andrews *et al.*, 1978). The results of those survival studies are summarized in fig. 5, where the log of the surviving cell fraction (Y axis) is plotted as a function of the UV dose (X axis). The 'normal zone' encompasses the survival curves of the 10 normal fibroblast strains studied (Andrews *et al.*, 1978; Barrett *et al.*, 1981). The 'early onset group A zone' encompasses the curves given by 5 patients with the early onset type of the juvenile onset form of XP neurological disease. As shown, the latter group of cells is so sensitive to the lethal effects of UV that after treatment with 3 J/m^2 they have approximately 1/10 000th of the survival of the comparably exposed normal cells.

At least 1 group A patient has cells which are relatively resistant to UV, as illustrated by the survival curve for patient XP8LO, a 6-yr-old XP patient without known neurological abnormalities. Intermediate between these extremes are the survival curves of the cells from XP12BE and XP1LO. While close in location, the curves from these 2 patients are statistically significantly different from one another (Andrews *et al.*, 1978). When the data points obtained in the present study for the fibroblast strain from XP19BE are plotted, the survival curve they determine is virtually indistinguishable from that for the XP1LO cells, but it is significantly higher than that for the XP12BE cells ($P = 0.003$).

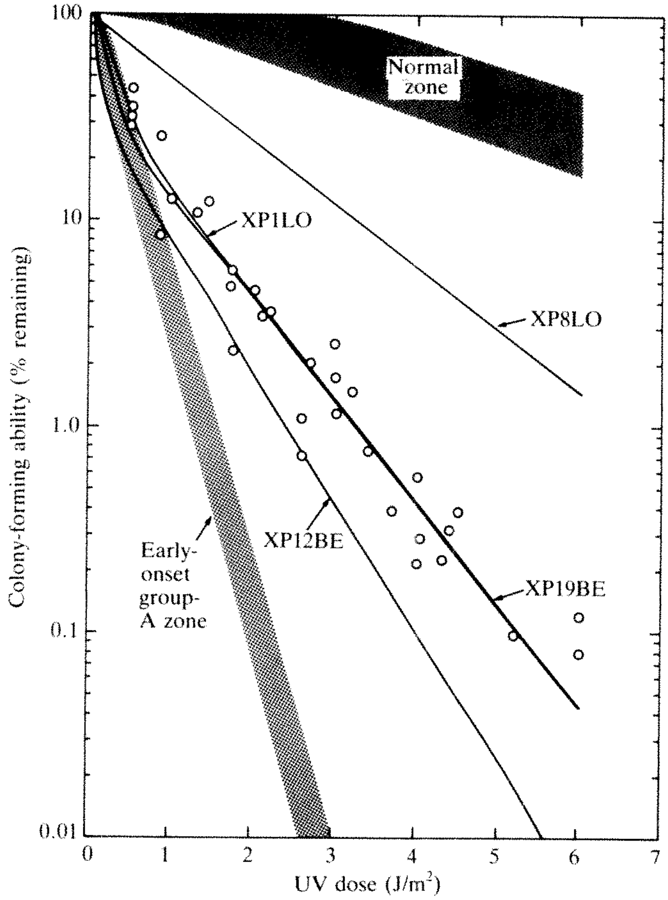

FIG. 5. Post-UV survival data points (○) and resulting survival curve of the fibroblast strain from *Case 2* (XP19BE) compared with the curves for other group A patients. The normal zone and the early onset group A zone contain the survival curves of 10 and 5 strains, respectively (*see* Methods). The more sensitive a strain, the less the amount of UV required to reduce its colony-forming ability to a given level. Another measure of the relative sensitivity of the strains is obtained by comparing the slopes of the exponential portions of the survival curves. The D_0 (J/m^2) survival parameter is the inverse of the slope and represents the dose of UV required to reduce the exponential portion by a set amount (*see* Methods). Thus the steepest slopes (which will have the smallest D_0 values) are manifested by the most sensitive strains. The D_0 survival parameter for the XP19BE survival curve is 0.83. To enable precise comparison with results in other laboratories, the D_0 values for the other curves have been recalculated by the method of Tarone *et al.* (1983) from the data used in Andrews *et al.* (1978) and are as follows: XP8LO, 1.45; XP1LO, 0.91; XP12BE, 0.69. The recalculated D_0 values for the 5 strains comprising the early onset group A zone are as follows: XP6TO, 0.29; XP4LO, 0.30; XP25RO, 0.29; XP26RO, 0.29; XPKFSF, 0.26.

DISCUSSION

The juvenile onset form of XP neurological disease

Early onset type. The first detailed description of XP neurological disease was that of De Sanctis and Cacchione (1932) who reported the clinical features of 3 severely affected young Italian brothers and the autopsy findings of 1 of them. The patients had severe growth retardation and gonadal hypoplasia. Subsequently, Silberstein (1938) described the clinical features of 2 brothers of Irish and German descent who had XP with a milder form of the neurological disease described by De Sanctis and Cacchione. His patients also had less somatic underdevelopment and apparently normal genitalia. Watanabe and Watanabe (1935) and Mitsuda (1940) reported the clinical features of several Japanese siblings with XP neurological disease. In 1950, Yano documented detailed clinical and necropsy findings on 2 of Mitsuda's patients. While it was not possible at the time to establish complementation group assignment of these patients, in retrospect it is likely that the Japanese patients were in XP complementation group A, since all studied Japanese patients with adequate evidence of XP neurological disease have been found to be in group A (Sugita *et al.*, 1977; Takebe *et al.*, 1977; Mitoh *et al.*, 1983; Kato *et al.*, 1985; Mimaki *et al.*, 1985, 1986, 1989; Origuchi *et al.*, 1987; Sato *et al.*, 1987; Tate *et al.*, 1987; Tachi *et al.*, 1988).

The neurological abnormalities of three series of Japanese group A patients have been described in detail: the 7-patient group of Sugita *et al.* (1977), the 12-patient group of Mitoh *et al.* (1983) and the extensive ongoing series of Mimaki *et al.* (1986, 1989) which currently consists of 35 patients. In addition, many case reports of the clinical abnormalities of smaller numbers of Japanese patients are also available (Reed *et al.*, 1965, 1969, 1977; Noto *et al.*, 1967; Handa *et al.*, 1978; Okayasu *et al.*, 1978; Fukuhara *et al.*, 1982; Hakamada *et al.*, 1982; Sasaki *et al.*, 1984; Mimaki *et al.*, 1985; Origuchi *et al.*, 1987; Tate *et al.*, 1987; Tachi *et al.*, 1988). With only one exception, all Japanese patients have had (either stated directly in the report or adduced from severity of disease) symptomatic onset before age 7 yrs (Mimaki *et al.*, 1985, 1986; Sato *et al.*, 1987). Some early onset cases can be milder than others, as clearly evidenced by the fourth case of Tachi *et al.* (1988) (previously described by Tate *et al.*, 1987). While the earliest signs are usually intellectual impairment and delayed motor development, all adequately followed Japanese patients have eventually developed the major neurological abnormalities listed in the Table (Yano, 1950; Noto *et al.*, 1967; Reed *et al.*, 1969; Sugita *et al.*, 1977; Handa *et al.*, 1978; Fukuhara *et al.*, 1982; Hakamada *et al.*, 1982; Mitoh *et al.*, 1983; Origuchi *et al.*, 1987; Tachi *et al.*, 1988). An apparently similar type of XP neurological disease, also beginning before age 7 yrs, occurs worldwide in non-Japanese group A XP patients (Reed *et al.*, 1965, 1969, 1977; Baden *et al.*, 1972; Kleijer *et al.*, 1973; der Kaloustian *et al.*, 1974; Pawsey *et al.*, 1979; Hashem *et al.*, 1980; Stefanini *et al.*, 1980). One group G English patient also became symptomatic before age 7 yrs (Arlett *et al.*, 1980). All such patients with symptomatic onset of their XP neurological disease prior to 7 yrs of age have the early onset type of the juvenile onset form of XP neurological disease (Robbins, 1989).

Intermediate onset type. XP neurological disease is not confined to the early onset type or to group A and group G patients. Two pairs of XP siblings, one in Bethesda (XP5BE, XP6BE) and the other in Newcastle (XP2NE, XP3NE), have been assigned to complementation group D (Robbins *et al.*, 1974; Kraemer *et al.*, 1975; de Weerd-Kastelein *et al.*, 1976). Their neurological disease has been reported in sufficient detail to establish that they have a progressive neurological degeneration identical to that of the early onset type of group A patients, except that symptomatic onset of XP neurological disease occurred some time between age 7 and 12 yrs (Robbins *et al.*, 1974; Thrush *et al.*, 1974; Longridge, 1976). At least 3 other group D patients in the

United States (Robbins *et al.*, 1974; Andrews *et al.*, 1978) and apparently 1 group G patient in England (Cheesbrough, 1978; Keijzer *et al.*, 1979) also have XP neurological disease with this later age of symptomatic onset. All these patients have been classified as having the intermediate age of onset type of the juvenile onset form of XP neurological disease (Robbins, 1989). Interestingly, the first patient to be described with XP neurological disease had the intermediate age of onset type (Neisser, 1883). A similar age of symptomatic onset has been observed in a patient from Czechoslovakia (Strian, 1966).

Late onset type. From the definition and occurrence of XP neurological disease presented above, it is evident that establishing a new age of onset type requires that the patients eventually develop the major neurological abnormalities which characterize XP neurological disease of the early onset type. This requirement is met by our patients XP12BE and XP19BE reported herein and also by patient XP1LO, who was reported in excellent detail by Kenyon *et al.* (1985). Of 15 major neurological findings present in the early onset type of XP neurological disease (Table), 14 were sought in our 2 patients (the electromyographic and biopsy study of muscle was not performed). Case 1 (XP12BE) has developed all 14 of these abnormalities. Case 2 (XP19BE), who is younger, has developed all but two of the abnormalities; he has not yet developed a frank dementia (although he already has intellectual impairment) or abnormal nerve conduction values apart from absent H reflexes (although he has clinical evidence of a peripheral neuropathy). Ten of the major neurological abnormalities were assessed in patient XP1LO who, as will be discussed, has the latest onset and mildest form of XP neurological disease among these 3 late onset type patients. She has 8 of these 10 abnormalities, lacking only extensor plantar responses and sensory deficits.

The neurological abnormalities in the Table are also relevant to an 11-yr-old, XP complementation group A Japanese patient, XP39OS (the 39th XP patient of the Osaka (OS) series), who was distinctive among 32 patients with XP neurological disease in having a much milder disease (Mimaki *et al.*, 1985, 1986; Sato *et al.*, 1987). While the patient may not yet be symptomatic, it is likely that she will become so during her

TABLE MAJOR ABNORMALITIES IN THE EARLY ONSET TYPE OF XP NEUROLOGICAL DISEASE*

Skull and brain size
  1. Microcephaly
  2. Brain atrophy

Cerebral dysfunction
  3. Intellectual impairment
  4. Cognitive deterioration (dementia)
  5. Abnormal EEG

Basal ganglia involvement
  6. Choreoathetosis

Cerebellar involvement
  7. Ataxia/dysmetria
  8 Dysarthria

Corticospinal tract involvement
  9. Extensor plantar response

Auditory involvement
  10 Sensorineural deafness

Peripheral neuropathy
  11. Hyporeflexia/areflexia
  12. Distal sensory deficits
  13. Abnormal Romberg test
  14 Abnormal nerve conduction studies
  15 Neuropathic EMG and muscle biopsy

* Based primarily on the clinical descriptions of Sugita *et al.* (1977), Mitoh *et al.* (1983) and Mimaki *et al.* (1986)

teenage years. Therefore, since she probably has the late onset type of the juvenile onset form of XP neurological disease, she illustrates the earliest neurological abnormalities of evolving XP neurological disease in such a patient. Of the 9 major abnormalities, including nerve conduction studies, sought in this child, she had 4 (intellectual impairment, extensor plantar responses, hyporeflexia, and a neuropathic electromyogram and muscle biopsy). Thus she has evidence of a peripheral neuropathy in the presence of normal nerve conduction studies. A similar constellation of areflexia and a neuropathic electromyogram and muscle biopsy in the presence of normal nerve conduction studies has been found for the 20 and 26-yr-old group D Bethesda sibling pair (Robbins *et al.*, 1974). XP19BE also has evidence of a peripheral neuropathy in the presence of normal nerve conduction studies apart from an absent H reflex. This may be the earliest detectable electrophysiological abnormality of the evolving peripheral neuropathy of XP neurological disease.

By searching for informative clinical comparisons between the 3 symptomatic late onset type patients, it is possible to determine the relative severity of their neurodegeneration. XP12BE has a more severe neurodegeneration than XP19BE: (1) she had areflexia at age 7 yrs when XP19BE was normoreflexic; and (2) she showed a more severe hearing loss at age 13 4/12 yrs than Case 2, even when he was 5 months older (fig. 1). XP12BE is also more severely affected than XP1LO: (1) she was areflexic by age 7 yrs, while XP1LO still had obtainable (albeit sluggish) reflexes at age 40 yrs; (2) she showed a more severe hearing loss by age 22 6/12 yrs than XP1LO at age 40 yrs (fig. 1); (3) she had a severe nerve conduction defect at age 22 yrs versus only a mild defect in XP1LO at age 40 yrs; and (4) she had extensor plantar responses and definitely decreased sensation by 22 yrs of age as compared with flexor responses and a normal sensory examination in XP1LO at age 40 yrs. Comparison between XP19BE and XP1LO is difficult because of lack of relevant information about XP1LO at younger ages. However, XP19BE appears to have a more severe neurodegeneration than XP1LO: (1) he had dysarthria by age 14 yrs, while XP1LO became dysarthric after age 31 yrs; and (2) he had progressed from normal reflexes at age 7 to severe hyporeflexia by age 14, while XP1LO had sluggish reflexes at age 40.

Asymptomatic XP neurological disease

A 17-yr-old black patient from Miami (XP1MI) was found to be in group C and to have mental retardation, microcephaly and a possibly neuropathic electromyogram (Robbins, 1978; Hananian and Cleaver, 1980). Although the tendon reflexes, nerve conduction studies, an EEG and an audiogram were normal, it is still possible that this patient may eventually develop XP neurological disease. Two neurologically asymptomatic group C patients (XP1BE, XP3BE) were found in their fourth decade to have slightly unsteady tandem gait (when deprived of visual sensory input) and slightly impaired rhythmic rapid alternating movements in the upper limbs (tendon reflexes and audiograms were normal) (Robbins *et al.*, 1983). A follow-up study was possible only for XP1BE 7 yrs later and showed progression of her neurological abnormalities: she then had total inability to perform tandem gait, markedly impaired rhythmic rapid alternating movements in both upper and lower extremities, hyporeflexia at the ankles and a 25 dB hearing loss bilaterally at 8 kHz (Robbins *et al.*, 1989). Thus XP1BE seems to have presymptomatic XP neurological disease, necessitating provision for an adult onset form of XP neurological disease (Robbins, 1989).

XP patients without XP neurological disease

While most XP patients with neurological disease are in complementation groups A and D, it is possible that not every patient in these groups is destined to develop neurological disease. For example, an Egyptian group A patient had no neurological abnormalities by age 35 yrs (Cleaver *et al.*, 1981), and Japanese group D patients have been described who had no evidence of XP neurological disease even by 65 yrs of age (Takebe *et al.*, 1977; Kato *et al.*, 1985; Mamada *et al.*, 1988; Ichihashi *et al.*, 1988). Similarly, the German group D patients so far described apparently have no neurological abnormalities (Fischer *et al.*, 1982). Furthermore, an unusual group A sibling pair has been reported from Italy: one patient had severe neurological disease, apparently of the early onset type, while the other had no evidence of neurological disease by age 21 yrs (Stefanini *et al.*, 1980). As Stefanini *et al.* (1980) suggested, it is possible that the unaffected sibling had some cells with higher UV-induced UDS than those of her affected brother and that these cells may have arisen from a back mutation at an early embryonic stage.

Most of the group C patients identified have no neurological abnormalities (Robbins *et al.*, 1974; Kraemer *et al.*, 1975; Bootsma, 1979; Pawsey *et al.*, 1979; Hashem *et al.*, 1980; Cleaver *et al.*, 1981; Fischer *et al.*, 1982; Fujiwara *et al.*, 1985, 1987). Additionally, no neurological disease has yet been detected in any of the 8 group E or 8 group F XP kindreds reported, despite the fact that the oldest patients were 50 and 64 yrs of age, respectively (Kondo *et al.*, 1989; Yamamura *et al.*, 1989). The third group G patient identified, in contrast to the first 2, had no evidence of neurological disease by age 37 yrs (Cheesbrough, 1978; Arlett *et al.*, 1980; Ichihashi *et al.*, 1985). Only 1 of numerous XP variant kindreds, including a patient as old as 87 yrs of age, had any neurological disease (Robbins *et al.*, 1974; Pawsey *et al.*, 1979; Fischer *et al.*, 1982; Kenyon *et al.*, 1985; Fujiwara *et al.*, 1987; Satoh and Nishigori, 1988). The 2 affected brothers of this unusual variant kindred, the oldest of whom was 42 yrs of age, had hyperreflexia and a low-frequency hearing deficit instead of the characteristic XP abnormalities of areflexia and high-frequency sensorineural deafness (Kenyon *et al.*, 1985). Thus this kindred can be considered to have a neurodegeneration other than the established form of XP neurological disease.

Two other patients with typical skin manifestations of XP have a neurodegeneration other than that of XP neurological disease (Robbins *et al.*, 1974; Brumback *et al.*, 1978; Robbins, 1988). Each patient has the neurological abnormalities of Cockayne syndrome, an autosomal recessive disease characterized by acute sun sensitivity, severe cachectic dwarfism, and characteristic facies and skeletal abnormalities (Guzzetta, 1972). Many of the neurological abnormalities of Cockayne syndrome (e.g., hyperreflexia, atypical retinitis pigmentosa, intracranial calcification, primary central and peripheral demyelination, and the triad of normal pressure hydrocephalus) do not occur in XP neurological disease. Each of these patients has a defect in DNA nucleotide-excision repair: 1 patient is the sole representative of XP complementation group B and the other of group H (Robbins, 1988). Because of the distinctive clinical features of these patients in having the typical skin manifestations of XP together with the typical neurological and other features of Cockayne syndrome, they have been classified as a distinct clinical entity, the 'XP-Cockayne syndrome complex' (Robbins, 1988).

DNA repair studies

UV-induced UDS of XP cells. On the basis of the inability of a cell strain to complement the cells of a reference strain representing a known XP complementation group, the cell strain is considered to be in the same complementation group as the reference strain (de Weerd-Kastelein *et al.*, 1972; Robbins *et al.*, 1974). Thus we can assign XP19BE to XP complementation group A, since his fibroblast strain did not complement the group A reference strain with regard to UV-induced UDS. This patient therefore becomes the third symptomatic patient in group A identified as having the late onset type of the juvenile onset form of XP neurological disease.

However, XP19BE is unusual in having 10% of the normal rate of UV-induced UDS. In contrast, most other group A patients have less than 2 to 3% of the normal rate of UV-induced UDS (for example, the other 2 late onset type group A patients (XP12BE and XP1LO), the asymptomatic 11-yr-old Japanese group A patient (XP39OS) with mild XP neurological disease, and numerous early onset type group A patients (Parrington *et al.*, 1971; der Kaloustian *et al.*, 1974; Kraemer *et al.*, 1975; Petinga *et al.*, 1977; Sugita *et al.*, 1977; Takebe *et al.*, 1977; Bootsma, 1979; Hashem *et al.*, 1980; Mimaki *et al.*, 1985; Sato *et al.*, 1987; Chang *et al.*, 1989)). Only 3 other group A patients have been convincingly reported to have more than minimal levels of UV-induced UDS. XP1BI has 10–15% of the normal rate and has no neurological abnormalities; unfortunately, however, the age of the patient was not reported (Bootsma, 1979). XP8LO (from London) has 36% of the normal rate (de Weerd-Kastelein *et al.*, 1976). Since she had no known neurological abnormalities when reported at age 6 yrs, it can be concluded that she did not have the early onset type of XP neurological disease, if, indeed, she is destined to develop XP neurological disease. XP1KU, a 7-yr-old Japanese girl with the early onset type of XP neurological disease, has somatic mosaicism for DNA-repair capacity in her fibroblast cultures: approximately 12% of her cells have levels of UV-induced UDS ranging from 37 to 55% of normal, while the remainder have the typical group A values of less than 3% (Chang *et al.*, 1989).

It is important to note that the level of UV-induced UDS in group A patients does not always correlate with the severity of neurological disease as measured by the rapidity of symptomatic onset. For example, while all the early onset type patients have minimal levels of such UDS, 2 (XP12BE and XP1LO) of the 3 late onset type patients also have these minimal levels (Petinga *et al.*, 1977). Furthermore, the 35-yr-old Egyptian group A patient who had no known neurological abnormalities and was of normal intelligence has this minimal level of UV-induced UDS (Cleaver *et al.*, 1981). Another example of noncorrelation is now provided by XP19BE: despite having considerably more UDS than XP1LO, his neurodegeneration is developing at an earlier age than did hers. Comparing UV-induced UDS levels with the severity of neurological disease in group A patients confirms similar findings concerning neurologically-affected group D patients: despite an intermediate age of symptomatic onset of XP neurological disease (i.e., 7–12 yrs of age), UDS levels are higher, and not lower, when compared with patients who do not develop XP neurological disease, for example, patients in group C (Robbins *et al.*, 1974; Kraemer *et al.*, 1975; Hashem *et al.*, 1980; Fujiwara *et al.*, 1981) and group F (Fujiwara *et al.*, 1981; Fujiwara and Satoh, 1985; Yamamura *et al.*, 1989). Clearly, relative UDS levels correlate neither with the occurrence of XP neurological disease nor its severity.

Survival of UV-treated XP cells. An excellent correlation, however, is found between the severity of neurological disease in the XP patients and the ability of their cultured fibroblast strains to survive and form colonies after treatment with UV (Andrews *et al.*, 1978; Barrett *et al.*, 1981). Strains from the early onset type group A patients are the most sensitive to killing by UV, while strains from the neurologically-affected intermediate onset type group D patients and group G patients are slightly less sensitive. Less sensitive still are the strains from XP12BE and XP1LO, followed by the group C and group F strains from patients who do not develop neurological disease (Andrews *et al.*, 1978; Fujiwara *et al.*, 1981). It should be noted, however, that the 3 neurologically affected, but still asymptomatic, group C patients (XP1MI, XP1BE, XP3BE) who, as previously discussed, will probably eventually develop symptomatic XP neurological disease, have the most sensitive of all group C fibroblast strains.

It is possible to consider the group A fibroblast strains in more detail. The strain from the Japanese group A patient XP39OS, who probably has the late onset type of the juvenile onset form of XP neurological disease, has more survival after treatment with UV than the strain from a Japanese group A patient with the typical early onset type of XP neurological disease (Sato *et al.*, 1987). Likewise, the group A fibroblast strain from a Japanese patient who has relatively mild neurological disease of the early onset type is also slightly more resistant to the lethal effects of UV than were the strains from 2 typical Japanese group A patients (Tate *et al.*, 1987; Tachi *et al.*, 1988).

Fig. 5 shows the survival curve we have established in the current study for the strain from XP19BE. Also shown are the zones containing the curves for the 10 normal and 8 group A fibroblast strains we have previously published (Andrews *et al.*, 1978; Barrett *et al.*, 1981). As is apparent, the survival of the XP19BE strain is in the range given by the strains from the 2 other late onset type group A patients, XP1LO and XP12BE. However, the XP12BE curve is significantly more sensitive to UV than either the XP1LO or the XP19BE curve ($P \leq 0.003$), correlating, therefore, with the fact that XP12BE has a more severe neurodegeneration than either XP1LO or XP19BE. Despite the fact that XP19BE probably has a slightly more severe neurodegeneration than XP1LO, the survival curves of their fibroblast strains are virtually superimposable and therefore not distinguishable from one another, indicating that this survival test cannot distinguish such minor differences in clinical severity. Considering, however, that the XP19BE curve could have been situated anywhere on the graph, it is remarkable that its location is so close to that from the XP patient who also had a very mild neurodegeneration.

DNA damage hypothesis of XP neurological disease

The relative ability of XP fibroblast strains to survive after treatment with UV depends on their ability to repair the UV-induced damage in their DNA to a functional state. While all XP patients in complementation group A presumably have defective expression of the group A gene product, different patients could have different mutations in the group A gene. Thus some group A patients may have no functional product from the group A gene, while others may have a gene product with partial activity. Considerations such as these can account for the fact that some group A patients have a very severe defect in DNA repair (resulting in marked killing of their cultured cells by UV in vitro), while others have a milder repair defect (resulting in less killing by UV in vitro) (fig. 5).

The neuronal DNA integrity theory of XP neurological disease has been proposed to explain how the DNA repair defect could cause the neurodegeneration which XP patients develop (Andrews *et al.*, 1978; Robbins, 1983, 1989). Briefly, the theory holds that transcribing genes in neurons are damaged by normal intracellular UV-mimetic metabolites, that the damage is not repaired because of the XP DNA repair defect, and that the neurons die when the unrepaired damage blocks transcription of the genes and, therefore, synthesis of proteins or other molecules necessary for neuron survival. Since neuron groups probably have different amounts and types of the incipient damage, those with relatively large amounts of the type of DNA damage which is the substrate for the defective DNA repair process accumulate the most unrepaired DNA and die, thereby accounting for the selective degeneration of certain neuron groups. The neuronal DNA integrity theory has been considered by Robbins (1983) to be applicable not only to neurons with typical action potentials but also to postmitotic excitable tissue without characteristic nerve impulses, for example, the hair cells of the cochlea, whose damage appears to be the initial cause of the sensorineural hearing loss in XP (Kenyon *et al.*, 1985). While many CNS changes in XP are clearly degenerative, some may be developmental (Yano, 1950). Even the latter could result from the faulty DNA repair postulated to occur (Andrews *et al.*, 1978) in the embryonic XP nervous system.

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REFERENCES

Andrews AD, Barrett SF, Robbins JH (1978) Xeroderma pigmentosum neurological abnormalities correlate with colony-forming ability after ultraviolet radiation. *Proceedings of the National Academy of Sciences of the USA,* **75**, 1984–1988.

Arlett CF, Harcourt SA, Lehmann AR, Stevens S, Ferguson-Smith MA, Morley WN (1980) Studies on a new case of xeroderma pigmentosum (XP3BR) from complementation group G with cellular sensitivity to ionizing radiation. *Carcinogenesis,* **1**, 745–751.

Baden HP, Parrington JM, Delhanty JDA, Pathak MA (1972) DNA synthesis in normal and xeroderma pigmentosum fibroblasts following treatment with 8-methoxypsoralen and long wave ultraviolet light. *Biochimica et Biophysica Acta,* **262**, 247–255.

Barrett SF, Tarone RE, Moshell AN, Ganges MB, Robbins JH (1981) The post-UV colony-forming ability of normal fibroblast strains and of the xeroderma pigmentosum group G strain. *Journal of Investigative Dermatology,* **76**, 59–62.

Bootsma D (1979) DNA repair deficiencies in man. In: *Radiation Research.* Edited by S. Okada, M. Imamura, T. Terashima and H. Yamaguchi. Tokyo: Japanese Association for Radiation Research, pp. 472–475.

Bootsma D, Keijzer W, Jung EG, Bohnert E (1989) Xeroderma pigmentosum complementation group XP-I withdrawn. *Mutation Research,* **218**, 149–151.

Brumback RA, Yoder FW, Andrews AD, Peck GL, Robbins JH (1978) Normal pressure hydrocephalus: recognition and relationship to neurological abnormalities in Cockayne's syndrome. *Archives of Neurology, Chicago,* **35**, 337–345.

Chang HR, Ishizaki K, Sasaki MS, Toguchida J, Kato M, Nakamura Y *et al.* (1989) Somatic mosaicism for DNA repair capacity in fibroblasts derived from a group A xeroderma pigmentosum patient. *Journal of Investigative Dermatology,* **93**, 460–465.

CHEESBROUGH MJ (1978) Xeroderma pigmentosum—a unique variant with neurological involvement. *British Journal of Dermatology*, **99**, Supplement 16, 61.

CLEAVER JE (1968) Defective repair replication of DNA in xeroderma pigmentosum. *Nature, London*, **218**, 652–656.

CLEAVER JE, ZELLE B, HASHEM N, EL-HEFNAWI MH, GERMAN J (1981) Xeroderma pigmentosum patients from Egypt: II. Preliminary correlations of epidemiology, clinical symptoms and molecular biology. *Journal of Investigative Dermatology*, **77**, 96–101.

DENCKLA MB (1985) Revised neurological examination for subtle signs (1985) *Psychopharmacology Bulletin*, **21**, 773–800, 1111–1124.

DER KALOUSTIAN VM, DE WEERD-KASTELEIN EA, KLEIJER WJ, KEIJZER W, BOOTSMA D (1974) The genetic defect in the De Sanctis-Cacchione syndrome. *Journal of Investigative Dermatology*, **63**, 392–396.

DE SANCTIS C, CACCHIONE A (1932) L'idiozia xerodermica. *Rivista Sperimentale di Freniatria e Medicina Legale delle Alienazioni Mentali*, **56**, 269–292.

DE WEERD-KASTELEIN EA, KEIJZER W, BOOTSMA D (1972) Genetic heterogeneity of xeroderma pigmentosum demonstrated by somatic cell hybridization. *Nature: New Biology, London*, **238**, 80–83.

DE WEERD-KASTELEIN EA, KEIJZER W, SABOUR M, PARRINGTON JM, BOOTSMA D (1976) A xeroderma pigmentosum patient having a high residual activity of unscheduled DNA synthesis after UV is assigned to complementation group A. *Mutation Research*, **37**, 307–312.

FISCHER E, THIELMANN HW, NEUNDÖRFER B, RENTSCH FJ, EDLER L, JUNG EG (1982) Xeroderma pigmentosum patients from Germany: clinical symptoms and DNA repair characteristics. *Archives of Dermatological Research*, **274**, 229–247.

FUJIWARA Y, KANO Y, PAUL P, GOTO K, YAMAMOTO K, MIYAZAKI N (1981) Excision and crosslink repair of DNA and sister chromatid exchanges in cultured human fibroblasts with different repair capacities. In: *Mutation, Promotion and Transformation In Vitro. GANN Monograph on Cancer Research*, Number 27. Edited by N. Inui, T. Kuroki, M.-A. Yamada and C. Heidelberger. Tokyo: Japan Scientific Societies Press, pp. 33–44.

FUJIWARA Y, ICHIHASHI M, UEHARA Y, MATSUMOTO A, YAMAMOTO Y, KANO Y *et al.* (1985) Xeroderma pigmentosum groups C and F: additional assignments and a review of the subjects in Japan. *Journal of Radiation Research*, **26**, 443–449.

FUJIWARA Y, SATOH Y (1985) Assignment of two Japanese xeroderma pigmentosum patients to complementation group D and their characteristics. *Japanese Journal of Cancer Research, Gann*, **76**, 162–166.

FUJIWARA Y, MATSUMOTO A, ICHIHASHI M, SATOH Y (1987) Heritable disorders of DNA repair: xeroderma pigmentosum and Fanconi's anemia. *Current Problems in Dermatology*, **17**, 182–198.

FUKUHARA N, KUMAMOTO T, TAKASAWA H, TSUBAKI T, ORIGUCHI Y (1982) The peripheral neuropathy in de Sanctis-Cacchione syndrome: histological, ultrastructural, and morphometric studies. *Acta Neuropathologica, Berlin*, **56**, 194–200.

GREULICH WW, PYLE SI (1959) *Radiographic Atlas of Skeletal Development of the Hand and Wrist*. Second edition. Stanford: Stanford University Press.

GUZZETTA F (1972) Cockayne-Neill-Dingwall syndrome. In: *Handbook of Clinical Neurology*, Volume 13. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, pp. 431–440.

HAKAMADA S, WATANABE K, SOBUE G, HARA K, MIYAZAKI S (1982) Xeroderma pigmentosum: neurological, neurophysiological and morphological studies. *European Neurology*, **21**, 69–76.

HAMILL PVV, DRIZD TA, JOHNSON CL, REED RB, ROCHE AF (1977) NCHS growth curves for children: birth-18 years: United States. *Vital and Health Statistics: Data from the National Health Survey*. Series 11, Number 165. DHEW Publication No. (PHS) 78-1650. Hyattsville, MD: US Department of Health, Education, and Welfare, Public Health Service, National Center for Health Statistics.

HANANIAN J, CLEAVER JE (1980) Xeroderma pigmentosum exhibiting neurological disorders and systemic lupus erythematosus. *Clinical Genetics*, **17**, 39–45.

HANDA J, NAKANO Y, AKIGUCHI I (1978) Cranial computed tomography findings in xeroderma pigmentosum with neurologic manifestations (De Sanctis-Cacchione syndrome). *Journal of Computer Assisted Tomography*, **2**, 456–459.

HASHEM N, BOOTSMA D, KEIJZER W, GREENE A, CORIELL L, THOMAS G *et al.* (1980) Clinical characteristics, DNA repair, and complementation groups in xeroderma pigmentosum patients from Egypt. *Cancer Research*, **40**, 13–18.

HOKKANEN E, IIVANAINEN M, WALTIMO O (1969) Zu den neurologischen Manifestationen des Xeroderma pigmentosum. *Deutsche Zeitschrift fur Nervenheilkunde*, **196**, 206–216.

ICHIHASHI M, FUJIWARA Y, UEHARA Y, MATSUMOTO A (1985) A mild form of xeroderma pigmentosum assigned to complementation group G and its repair heterogeneity. *Journal of Investigative Dermatology*, **85**, 284–287.

ICHIHASI M, YAMAMURA K, HIRAMOTO T, FUJIWARA Y (1988) No apparent neurologic defect in a patient with xeroderma pigmentosum complementation group D. *Archives of Dermatology*, **124**, 256–260.

KATO T, AKIBA H, SEIJI M, TOHDA H, OIKAWA A (1985) Clinical and biological studies of 26 cases of xeroderma pigmentosum in northeast district of Japan. *Archives of Dermatological Research*, **277**, 1–7.

KEIJZER W, JASPERS NGJ, ABRAHAMS PJ, TAYLOR AMR, ARLETT CF, ZELLE B *et al.* (1979) A seventh complementation group in excision-deficient xeroderma pigmentosum. *Mutation Research*, **62**, 183–190.

KENYON GS, BOOTH JB, PRASHER DK, RUDGE P (1985) Neuro-otological abnormalities in xeroderma pigmentosum with particular reference to deafness. *Brain*, **108**, 771–784

KLEIJER WJ, DE WEERD-KASTELEIN EA, SLUYTER ML, KEIJZER W, DE WIT J, BOOTSMA D (1973) UV-induced DNA repair synthesis in cells of patients with different forms of xeroderma pigmentosum and of heterozygotes. *Mutation Research*, **20**, 417–428.

KOLLER PC (1948) Inheritance of xeroderma and its chromosome mechanism. *British Journal of Cancer*, **II**, 149–155.

KONDO S, MAMADA A, MIYAMOTO C, KEONG C-H, SATOH Y, FUJIWARA Y (1989) Late onset of skin cancers in 2 xeroderma pigmentosum group F siblings and a review of 30 Japanese xeroderma pigmentosum patients in groups D, E and F. *Photodermatology*, **6**, 89–95.

KRAEMER KH, COON HG, PETINGA RA, BARRETT SF, RAHE AE, ROBBINS JH (1975) Genetic heterogeneity in xeroderma pigmentosum: complementation groups and their relationship to DNA repair rates. *Proceedings of the National Academy of Sciences of the USA*, **72**, 59–63.

KRAEMER KH, DIGIOVANNA JJ, MOSHELL AN, TARONE RE, PECK GL (1988) Prevention of skin cancer in xeroderma pigmentosum with the use of oral isotretinoin. *New England Journal of Medicine*, **318**, 1633–1637.

LEWIS PD, MCLAUGHLIN J, THOMAS PK (1978) Neurological manifestations in xeroderma pigmentosum: case report with pathological findings. *Archives Suisses de Neurologie, Neurochirurgie et de Psychiatrie*, **123**, 96.

LONGRIDGE NS (1976) Audiological assessment of deafness associated with xeroderma pigmentosum. *Journal of Laryngology and Otology*, **90**, 539–551.

MAMADA A, KONDO S, KAWADA A, SATOH Y, FUJIWARA Y (1988) Delayed sensorineural deafness and skin carcinogenesis in a Japanese xeroderma pigmentosum group D patient. *Photodermatology*, **5**, 83–91.

MIMAKI T, SATO K, KOZUKA T, IKENAGA M, ITO N, TAGAWA T *et al.* (1985) A case of group-A xeroderma pigmentosum with mild neurological symptoms. *Shonika Shinryo (Journal of Pediatric Practice)*, **48**, 1304–1307 (in Japanese).

MIMAKI T, ITOH N, ABE J, TAGAWA T, SATO K, YABUUCHI H *et al.* (1986) Neurological manifestations in xeroderma pigmentosum. *Annals of Neurology*, **20**, 70–75.

MIMAKI T, TAGAWA T, TANAKA J, SATO K, YABUUCHI H (1989) EEG and CT abnormalities in xeroderma pigmentosum. *Acta Neurologica Scandinavica*, **80**, 136–141.

MITOH Y, KOBAYASI Y, SATOH Y, IWAKAWA Y (1983) Neuropathy in group A xeroderma pigmentosum patients. *Hifuka No Rinsho (Rinsho Derma)*, **25**, 347–352 (in Japanese).

MITSUDA H (1940) On the simultaneous occurrence of xeroderma pigmentosum and encephalopathy. *Seishin Shinkeigaku Zasshi (Psychiatria et Neurologia Japonica)*, **44**, 55–62 (in Japanese).

NEISSER A (1883) Ueber das 'Xeroderma pigmentosum' (Kaposi), liodermia essentialis cum melanosi et telangiectasia. *Vierteljahresschrift für Dermatologie und Syphilis, Wien*, **10**, 47–62.

NOTO C, KAMOYA S, HOSHI J, AOKI K (1967) Xeroderma pigmentosum complicated with brain symptoms. *Seishin Shinkeigaku Zasshi (Psychiatria et Neurologia Japonica)*, **69**, 539–544 (in Japanese).

OGAWA H, OHAMA E, KUMANISHI T, OYAKE Y, KATAGIRI T, NAGASHIMA T (1976) Neuropathologic examination of an autopsy case of De Sanctis-Cacchione syndrome of xeroderma pigmentosum. *Shinkei Kenkyu No Shimpo (Advances in Neurological Sciences)*, **20**, 434–442 (in Japanese).

OKAYASU I, SATOH Y, IRIMAJIRI T, MITOH Y (1978) Fetal case of xeroderma pigmentosum: first report of an autopsy case. *Acta Pathologica Japonica, Tokyo*, **28**, 459–464.

ORIGUCHI Y, EDA I, MATSUMOTO S, FURUSE A (1987) Quantitative histologic study of sural nerves in xeroderma pigmentosum. *Pediatric Neurology*, **3**, 356–359.

PARRINGTON JM, DELHANTY JDA, BADEN HP (1971) Unscheduled DNA synthesis, u.v.-induced chromosome aberrations and SV_{40} transformation in cultured cells from xeroderma pigmentosum. *Annals of Human Genetics, London*, **35**, 149–160.

PAWSEY SA, MAGNUS IA, RAMSAY CA, BENSON PF, GIANNELLI F (1979) Clinical, genetic and DNA repair studies on a consecutive series of patients with xeroderma pigmentosum. *Quarterly Journal of Medicine*, **48**, 179–210.

PETINGA RA, ANDREWS AD, TARONE RE, ROBBINS JH (1977) Typical xeroderma pigmentosum complementation group A fibroblasts have detectable ultraviolet light-induced unscheduled DNA synthesis. *Biochimica et Biophysica Acta*, **479**, 400–410.

REED WB, MAY SB, NICKEL WR (1965) Xeroderma pigmentosum with neurological complications: the de Sanctis-Cacchione syndrome. *Archives of Dermatology*, **91**, 224–226.

REED WB, LANDING B, SUGARMAN G, CLEAVER JE, MELNYK J (1969) Xeroderma pigmentosum: clinical and laboratory investigation of its basic defect. *Journal of the American Medical Association*, **207**, 2073–2079.

REED WB, SUGARMAN GI, MATHIS RA (1977) DeSanctis-Cacchione syndrome: a case report with autopsy findings. *Archives of Dermatology*, **113**, 1561–1563.

ROBBINS JH (1978) Significance of repair of human DNA: evidence from studies of xeroderma pigmentosum. *Journal of the National Cancer Institute*, **61**, 645–656.

ROBBINS JH (1983) Hypersensitivity to DNA-damaging agents in primary degenerations of excitable tissue. In: *Cellular Responses to DNA Damage*. Edited by E. C. Friedberg and B. A. Bridges. New York: Alan R. Liss, pp. 671–700.

ROBBINS JH (1987*a*) Xeroderma pigmentosum. In: *Neurocutaneous Diseases: A Practical Approach*. Edited by M. R. Gomez. Boston and London: Butterworths, pp. 118–127.

ROBBINS JH (1987*b*) Progressive sensorineural deafness in xeroderma pigmentosum: its evaluation and cause. *Clinical Research*, **35**, 795A.

ROBBINS JH (1988) Xeroderma pigmentosum: defective DNA repair causes skin cancer and neurodegeneration. *Journal of the American Medical Association*, **260**, 384–388.

ROBBINS JH (1989) A childhood neurodegeneration due to defective DNA repair: a novel concept of disease based on studies of xeroderma pigmentosum. *Journal of Child Neurology*, **4**, 143–146.

ROBBINS JH, KRAEMER KH, LUTZNER MA, FESTOFF BW, COON HG (1974) Xeroderma pigmentosum: an inherited disease with sun sensitivity, multiple cutaneous neoplasms, and abnormal DNA repair. *Annals of Internal Medicine*, **80**, 221–248.

ROBBINS JH, POLINSKY RJ, MOSHELL AN (1983) Evidence that lack of deoxyribonucleic acid repair causes death of neurons in xeroderma pigmentosum. *Annals of Neurology*, **13**, 682–684.

ROBBINS JH, MEER J, CARL J, SONIES BC (1987) Late development of neurologic abnormalities (NA) in xeroderma pigmentosum (XP): a primary neuronal degeneration caused by defective repair of neuronal DNA. *Neurology, Cleveland*, **37**, Supplement 1, 87.

ROBBINS JH, BRUMBACK RA, MOSHELL AN (1989) Xeroderma pigmentosum neurologic disease in a complementation group C patient. *Clinical Research*, **37**, 114A.

RÖYTTÄ M, ANTTINEN A (1986) Xeroderma pigmentosum with neurological abnormalities. A clinical and neuropathological study. *Acta Neurologica Scandinavica*, **73**, 191–199.

SASAKI K, OKUYAMA T, TACHI N, JO M, SHINODA M (1984) An autopsy case of De Sanctis-Cacchione syndrome. *Shinkei Naika (Neurological Medicine)*, **21**, 343–349 (in Japanese).

SATO K, WATATANI M, IKENAGA M, KOSUKA T, KITANO Y, YOSHIKAWA K *et al.* (1987) Sensitivity to UV radiation of fibroblasts from a Japanese group A xeroderma pigmentosum patient with mild neurological abnormalities. *British Journal of Dermatology*, **116**, 101–108.

SATOH Y, NISHIGORI C (1988) Xeroderma pigmentosum: clinical aspects. In: *Genetics of Human Tumors in Japan. GANN Monograph on Cancer Research*, No. 35. Edited by H. Takebe and J. Utsunomiya. Tokyo: Japan Scientific Societies Press and London: Taylor and Francis, pp. 113–126.

SILBERSTEIN AG (1938) Xeroderma pigmentosum with mental deficiency: a report of 2 cases. *American Journal of Diseases of Children*, **55**, 784–791.

SMITHERS DW, WOOD JH (1952) Xeroderma pigmentosum: an attempt at cancer prophylaxis. *Lancet*, **i**, 945–946.

STEFANINI M, KEIJZER W, DALPRÀ L, ELLI R, PORRO MN, NICOLETTI B *et al.* (1980) Differences in the levels of UV repair and in clinical symptoms in two sibs affected by xeroderma pigmentosum. *Human Genetics*, **54**, 177–182.

STRIAN F (1966) Kasuistischer Beitrag zur xerodermalen Idiotie: de Sanctis-Cacchione Syndrom. *Deutsche Zeitschrift für Nevenheilkunde*, **189**, 218–230.

SUGITA T, SUMI S, MATSUMOTO Y, MIMAKI K, YABUUCHI M, SHIMIZU H *et al.* (1977) Study of peripheral neuropathy in seven cases of xeroderma pigmentosum with neurological symptoms. *No To Hattatsu (Official Journal of the Japanese Society of Child Neurology)*, **9**, 276–282 (in Japanese).

TACHI N, SASAKI K, KUSANO T, WAKAI S, NAGAOKA M, ANNAKA S *et al.* (1988) Peripheral neuropathy in four cases of group A xeroderma pigmentosum. *Journal of Child Neurology*, **3**, 114–119.

TAKEBE H, MIKI Y, KOZUKA T, FURUYAMA J, TANAKA K, SASAKI MS *et al.* (1977) DNA repair characteristics and skin cancers of xeroderma pigmentosum patients in Japan. *Cancer Research*, **37**, 490–495.

TARONE RE, SCUDIERO DA, ROBBINS JH (1983) Statistical methods for in vitro cell survival assays. *Mutation Research*, **111**, 79–96.

TATE N, SASAKI K, KUSANO T, WATANABE Y, WAKAI S, KAMEDA K *et al.* (1987) A case of group-A xeroderma pigmentosum. *No To Hattatsu (Official Journal of the Japanese Society of Child Neurology)*, **19**, 254–256 (in Japanese).

THRUSH DC, HOLTI G, BRADLEY WG, CAMPBELL MJ, WALTON JN (1974) Neurological manifestations of xeroderma pigmentosum in two siblings. *Journal of the Neurological Sciences*, **22**, 91–104.

WATANABE E, WATANABE H (1935) Familial encephalopathy with xeroderma pigmentosum. *Seishin Shinkeigaku Zasshi (Psychiatria et Neurologia Japonica)*, **38**, 466–485 (in Japanese).

YAMAMURA K, ICHIHASHI M, HIRAMOTO T, OGOSHI M, NISHIOKA K, FUJIWARA Y (1989) Clinical and photobiological characteristics of xeroderma pigmentosum complementation group F: a review of cases from Japan. *British Journal of Dermatology*, **121**, 471–480.

YANO K (1950) Xeroderma Pigmentosum mit Störungen des Zentralnervensystems; eine Histopathologische Untersuchung. *Folia Psychiatrica et Neurologica Japonica*, **4**, 143–175.

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APPENDIX

Summary of Wechsler Intelligence Scale Testing

	Patient XP12BE			*Patient XP19BE*	
Test	*WISC-R*	*WISC-R*	*WAIS-R*	*WISC-R*	*WISC-R*
Age (yrs) at testing	*15 2/12*	*17 4/12*	*17 8/12*	*11 7/12*	*13 10/12*
Verbal IQ	78	77	78	82	75
Performance IQ	84	78	72	91	92
Full Scale IQ	79	76	74	85	82
Information	9	6	5	8	5
Similarities	5	5	7	7	7
Arithmetic	6	6	5	8	8
Vocabulary	7	7	5	7	6
Comprehension	5	7	4	6	4
Digit span	4	4	6	7	9
Picture completion	9	10	6	11	7
Picture arrangement	5	7	5	8	9
Block design	6	5	5	8	10
Object assembly	7	–	6	–	13
Mazes	11	–	–	–	10
Coding	–	5	–	8	6
Digit symbol	–	–	6	–	–

WISC-R = Wechsler Intelligence Scale for Children, Revised; WAIS-R = Wechsler Adult Intelligence Scale, Revised.

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NERVE CELL LOSS IN THE THALAMUS IN ALZHEIMER'S DISEASE AND PARKINSON'S DISEASE

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SUMMARY

Serial sections through the thalamus from the fixed right cerebral hemispheres of 15 cases (5 Parkinson's disease, 5 Alzheimer's disease (AD) and 5 controls) were used to obtain quantitative estimates of neuronal loss, neurofibrillary tangle formation and Lewy body inclusions within individual thalamic nuclei. Severe neuronal loss and tangle formation were evident in the anterodorsal nucleus from the AD cases. Nerve cell damage was also present in the centromedian nucleus but was not associated with tangle formation and occurred in all but 2 of the brains examined. It is likely that the anterodorsal neurons are damaged locally by the Alzheimer's disease process whereas the changes in the centromedian nucleus may be related to ageing.

INTRODUCTION

Alzheimer's disease (AD) and Parkinson's disease (PD) each show distinctive neuropathological features. Neuritic plaques and neurofibrillary tangle formation in the cerebral cortex characterize AD (Tomlinson and Corsellis, 1984) whereas the principal lesion in PD consists of nerve cell loss and Lewy body formation in the substantia nigra (Oppenheimer, 1984). On the other hand, there is a striking similarity in the distribution of extranigral subcortical pathology in both these disorders. Indeed, pathological changes in the cholinergic nuclei of the basal forebrain (Whitehouse *et al.*, 1981, 1983; Arendt *et al.*, 1983; Candy *et al.*, 1983), the noradrenergic locus coeruleus (Forno, 1978; Mann *et al.*, 1980, 1983; Tomlinson *et al.*, 1981; Bondareff *et al.*, 1982) and the mesencephalic dorsal raphe nucleus (Ishii, 1966; Escourolle *et al.*, 1971; Jellinger, 1987) occur in both AD and PD. Although the thalamus has reciprocal connections with the striopallidal complex and the entire cerebral cortex (Carpenter and Sutin, 1983) and also receives projections from the basal forebrain nuclei, the dorsal raphe nucleus and the locus coeruleus (Nieuwenhuys, 1985), it has not been subjected to detailed study.

Vogt and Vogt (1941) and Simma (1949, 1951) published purely descriptive accounts of the pathological changes seen in the thalamus in cases of AD, but with conflicting results. Vogt and Vogt (1941) found nerve cell degeneration and reactive gliosis in the centromedian nucleus in intellectually normal elderly controls and in cases of AD. They

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observed these changes at an earlier age in the AD cases. The Vogts suggested that nerve cell loss in the centromedian nucleus was a primary ageing phenomenon that occurred prematurely in AD. Simma (1949) could not reproduce these observations. On the other hand, he found nerve cell loss in the anterior, mediodorsal and lateral posterior nuclei and in the pulvinar in AD (Simma, 1951). He concluded that these thalamic changes represented retrograde degeneration secondary to the severe frontal and parietal cortical pathology.

There has been no subsequent quantitative work to establish whether or not there is significant nerve cell loss in the thalamus in AD. We report here the results of nerve cell counts in individual thalamic nuclei and the subthalamic nucleus from cases of AD, PD and from elderly controls.

MATERIAL AND METHODS

Cases studied

Five cases of AD and 5 cases of PD were selected randomly from a collection of cases with these diagnoses at Newcastle General Hospital that came to autopsy between February 1983 and January 1986. They were compared with 5 control cases that had had no evidence of cognitive impairment or motor difficulties in life; they were selected to provide a satisfactory match with the AD and PD groups separately with regard to age at death. No attempt was made to match the two disease groups for age and the mean age at death in the PD group was a decade lower than that of the AD group. Two of the controls died from the local complications of bronchogenic carcinoma. Another had breast cancer and died from hepatic portal venous thrombosis and intestinal infarction. The respective causes of death in the other 2 control cases were lobar pneumonia and pulmonary embolism.

Table 1 shows the pertinent clinical and pathological details for the normal controls, the PD and the AD cases. The control brains showed no significant degree of neocortical senile plaques or substantia nigra cell loss. Recent infarction of the striate cortex was present in 1 case but the total volume of softening was only 12 ml. The PD cases were characterized by severe nerve cell loss in the substantia nigra associated with Lewy body formation. Two cases did have a significant degree of neuritic plaque formation in neocortex but with only a very occasional neurofibrillary tangle. These latter cases were not regarded as having coincidental AD. Indeed, Tomlinson *et al.* (1968) have demonstrated that remarkably large numbers of plaques may occur throughout the neocortex in intellectually normal subjects and only the combination with numerous neocortical tangles allows such a diagnosis. Both of these PD patients and 1 other (with no neocortical plaque formation) had shown evidence of mild to moderate cognitive impairment. Cortical Lewy bodies were very rarely seen in these 3 cases but all had significant nerve cell loss in the basal forebrain nucleus of Meynert. Apart from a moderate to severe loss of pigmented neurons from the locus coeruleus in all the PD cases, there was no other pathology. The diagnosis of AD was made when extensive neuritic plaque formation in neocortex (equivalent to density measurements of $\geq 14/1.4$ mm^2; Tomlinson *et al.*, 1968) was combined with numerous neocortical neurofibrillary tangles (Tomlinson *et al.*, 1970). These cases showed a moderate to severe degree of nerve cell loss in the locus coeruleus and the nucleus of Meynert. The raphe nuclei of the midbrain and rostral pons contained variable numbers of neurofibrillary tangles. There was no significant nigral cell loss and Lewy bodies were absent. Microscopical examination showed an area of recent infarction of the parafascicular nucleus and part of the adjacent centromedian nucleus in the thalamus of 1 AD case. No other significant neuropathology was identified in the AD cases which had all been moderately to severely demented in life.

Tissue preparation

The intact right cerebral hemisphere, the brainstem and cerebellum from each case were fixed in formalin for 6 wks. After fixation, the hemisphere was cut into serial coronal slices of 0.75 cm thickness and examined macroscopically. Blocks from frontal, temporal, parietal and occipital cortex as well as blocks from midbrain, pons, medulla and cerebellum were processed and embedded in paraffin wax. Three sections were taken from each paraffin block of tissue and stained with a combined cresyl violet and myelin stain (Klüver

TABLE 1 CLINICAL AND PATHOLOGICAL DETAILS OF 15 POST-MORTEM CASES

	Normal	*Parkinson's disease*	*Alzheimer's disease*
Number	5	5	5
Age (yrs, mean ± SD)	78 ± 9	70 ± 7	80 ± 4
Sex	2M 3F	All M	1M 4F
Dementia*	None	Present in 3	Present in all
Akinesia/rigidity	None	All	None
Brain weight (g) (mean ± SD)	1290 ± 153	1400 ± 96	1091 ± 123
Neocortical plaques (per 1 4 mm^2)	<3 in all	None in 3 cases, >14 in 2 cases	>14 in all
Neocortical tangles	None in 2 cases, v. occas. in 3	None in 3 cases, v. occas. in 2	Numerous
Substantia nigra cell loss	None in 3 cases, slight in 2	Severe	None

* The presence and severity of dementia in life were assessed using the Blessed Dementia Scale and Mental Test Score (Blessed *et al* , 1968) in addition to the broader criteria in DSM III (American Psychiatric Association, 1980).

and Barrera, 1953), haematoxylin and eosin, and the modified Palmgren technique (Cross, 1982). Another 4 blocks of formalin-fixed tissue were taken from frontal, temporal, parietal and occipital cortex. Sections from these blocks were impregnated with silver using the von Braunmühl technique (von Braunmühl, 1928, 1931) to demonstrate neuritic plaques. The mean plaque density in these 4 sections was used as a diagnostic criterion for AD.

The thalamus and adjacent lentiform and subthalamic nuclei were dissected en bloc from each slice, processed and embedded in paraffin wax and 20 μm serial sections were cut. Cytoarchitectonic boundaries of individual nuclei were identified using a pair of sections at 1000 μm intervals. The first of each pair was lightly stained with cresyl violet and used for morphometric analysis. An adjacent section was stained with cresyl violet and Luxol fast blue (Klüver and Barrera, 1953) to aid the delineation of nuclear boundaries. Precise nuclear mapping required the application of cytoarchitectonic criteria which included the size and staining intensity of nerve cell bodies and the relative neuronal density between one thalamic nucleus and another (Andrew and Watkins, 1969; Hassler *et al.*, 1979; Jones, 1985). The thalamic nuclei were outlined on the cresyl violet sections by small dots of waterproof black ink using a binocular dissecting microscope at a magnification of ×10 or ×16.

Nuclear volumes

Fig. 1 shows how the volume of each thalamic nucleus, or of the thalamus as a whole, was calculated from these 'mapped' sections. The mediodorsal nucleus is used as an example in the diagram The cross-sectional area of each nucleus included on each section was measured using a Magiscan 2A image analysis system (Joyce-Loebl, Gateshead, Tyne and Wear, UK). The product of the area (in mm^2) and the distance from that section to the next gives the volume of that part of the relevant nucleus between the 2 sections. As this distance is 1 mm, the volume has the same numerical value as the area and so simply adding the area measurements gives the total volume for that nucleus.

In man, the anterodorsal nucleus consists of only a thin lamina of cells lying beneath the dorsomedial

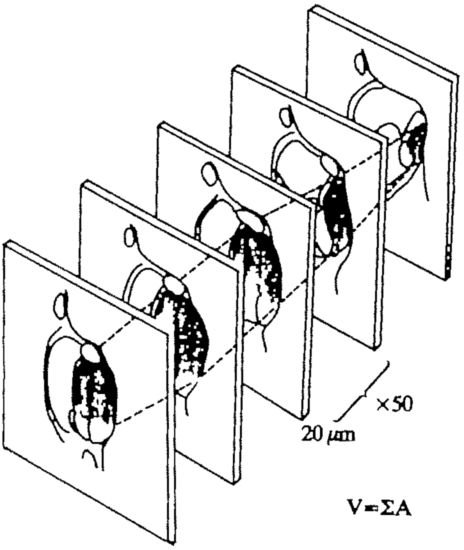

FIG. 1. Schematic drawing to illustrate the method for calculation of the volume of the mediodorsal nucleus based on semiserial coronal sections at 1 mm intervals. V = total volume of the mediodorsal nucleus in mm^3; ΣA = sum of the cross-sectional area measurements of the mediodorsal nucleus obtained from coronal sections at 1 mm intervals.

surface of the anterior tubercle in coronal sections. Neuronal counting in this submucleus was made by counting every nerve cell body in each section rather than by simply obtaining neuronal density measurements. It therefore was not necessary to measure the volume of the anterodorsal nucleus.

Neuronal counts

Neuronal counts were made from a high power field area of 0.44 mm^2 (magnification ×250). The focus was continually adjusted so that every neuronal nucleolus (nucleolated neuron) within the 20 μm thick section was counted. Counts were made from as many as 5 microscope fields for each thalamic nucleus included in that coronal section if the nucleus was sufficiently large. The smaller nuclei in cross-section would only allow counts within one or two fields. A preliminary analysis established that every fiftieth section could be counted without forsaking accuracy. This interval also proved convenient when it came to converting neuronal density values into an estimate of the total neuronal population in each individual thalamic nucleus.

The total number of neurons in each thalamic nucleus was calculated from the following formula: number of neurons (n) = D×area/0.44. 'D' is the mean of the cell density counts (2–5) in a high power field of 0.44 mm^2. In reality the value 'n' represents the neurons found within a short cylinder of tissue as each section is 20 μm thick. The cylinder of nucleus caudal to each stained and counted section is 50×20 μm long. Therefore, the value 'n' multiplied by 50 would represent the *total* number of neurons (N) in that volume of the particular nucleus between one counted section and the next. The sum of the values obtained for each series of 50 sections which included the relevant thalamic nucleus gives an estimate of the total number of neurons in that thalamic nucleus: Σ (N×50).

Tangle counts

A 20 μm thick paraffin tissue section was set aside at intervals of 2000 μm for the demonstration of neurofibrillary tangles. The silver method used was the modified Palmgren method of Cross (1982). The boundaries of the individual thalamic nuclei were marked out in fine waterproof ink. These boundaries were localized by superimposing the silver impregnated glass-mounted section on the adjacent 'mapped' cresyl violet-stained section. When the 2 slides were placed on an x-ray viewing box, the markings on the bottom slide were easily seen through the dark brown silver preparation and it was both simple and accurate to trace over these markings

Tangles were counted using a method similar to neuronal counting. The mean number of tangle-bearing neurons in 2–5 high-power microscope fields (each with an area of 0.44 mm^2) was obtained for each thalamic nucleus so giving a value for the density of 'tangled neurons' Extracellular tangles were not counted. These values were directly related to the neuronal density values for each nucleus obtained from the adjacent Nissl section so as to give the proportion of neurons that contained tangles in that nucleus:

$$\frac{\text{Proportion of tangled}}{\text{neurons in a nucleus}} = \frac{\text{Mean of 'tangled-neuron' counts in } 5\times0.44 \text{ mm}^2}{\text{Mean of neuronal counts in } 5\times0.44 \text{ mm}^2} \times 100$$

Statistical analysis

One-way analysis of variance was used to test the significance of any differences in thalamic neuronal counts and nuclear volumes between cases in the PD and AD groups and the control cases. Tables 2 and 3 show some 30 separate tests and it is quite likely that one or two of the results will reach 'significance' at the 5% (or 1 in 20) level purely by chance. Therefore, only differences shown to be statistically significant at the 1% level ($P < 0.01$) were considered to have clinical and pathological relevance.

RESULTS

Nuclear volumes

Table 2 shows the volume measurements for the individual thalamic nuclei, the subthalamic nucleus and the entire dorsal thalamus in the normal controls, the PD cases, and the AD cases. In 1 PD case the medial part of the rostral thalamus was not well covered on coronal tissue sections of the thalamus so that no volume measurements were possible on the parataenial, paraventricular and central medial nuclei. Statistical data for these nuclei are therefore based on measurements in 4 cases only. In 1 case of AD a small area of infarction within the thalamus occupied the centromedian and parafascicular nuclei. Therefore statistical data for these nuclei are also based on 4 cases.

The principal finding consists of a significant reduction ($P = 0.003$) in the total volume of the dorsal thalamus in AD (fig. 2). The process of generalized cerebral atrophy that characterizes this disease therefore does not spare the thalamus. No single individual nucleus of the dorsal thalamus appears to be solely responsible for the reduced volume of the whole thalamus. Although there were differences in the mean volume of parts of the anterior (external part) and posterior (caudal part) ventral lateral nuclei (reductions of 28% and 50%, respectively) and in the volume of the ventral posteromedial nucleus (a reduction of 35%), these differences did not achieve statistical significance ($P > 0.01$) and they applied to both the PD and the AD groups and not to one or other alone. The reticular nucleus stands out as the only individual nucleus apparently showing a significant ($P = 0.004$) reduction in volume in AD (fig. 3). Interestingly, the subthalamic nucleus showed a reduction in volume in AD but not in PD. However, this difference was not statistically significant ($P > 0.01$).

Neuron counts

Table 3 shows the neuron counts from the individual thalamic nuclei and the subthalamic nucleus in normal controls, PD and AD, respectively. In 1 PD case the medial part of the rostral thalamus was not covered on coronal sections of the thalamus so that no data could be obtained for the parataenial, paraventricular and central medial nuclei. Statistical data for these nuclei are therefore based on counts in 4 cases only. In 1 AD case the caudal intralaminar nuclei were the site of old cerebral infarction. The statistical data for the centromedian and parafascicular nuclei are also based on counts obtained from 4 cases.

Striking nerve cell loss was seen only in the anterodorsal division of the anterior nuclear

TABLE 2 VOLUME MEASUREMENTS (mm^3) FOR INDIVIDUAL THALAMIC NUCLEI, THE SUBTHALAMIC NUCLEUS AND THE WHOLE DORSAL THALAMUS BASED ON SEMISERIAL PARAFFIN SECTIONS FROM 5 CONTROLS, 5 PD CASES AND 5 AD CASES

	Nuclear volume (mm^3)		
Nucleus	*Normal (mean ± SEM)*	*Parkinson's disease (mean ± SEM)*	*Alzheimer's disease (mean ± SEM)*
Principal anterior	99.2 ± 5.6	100 ± 12.7	83.2 ± 4.8
Anterodorsal	—	—	—
Lateral dorsal	66.2 ± 3.6	53.6 ± 7.9	47.6 ± 4.0
Lateral posterior	95.8 ± 29.2	134.2 ± 39.6	125.2 ± 18.2
Ventral anterior	98.2 ± 13.9	81.6 ± 12.8	94.2 ± 8.5
Anterior ventral lateral.			
External part	179.2 ± 15.7	131.0 ± 8.2	130.4 ± 10.9
Internal part	114.0 ± 12.6	86.6 ± 17.9	78.0 ± 18.0
Principal ventral medial	17.2 ± 8.7	9.6 ± 3.9	6.0 ± 1.8
Posterior ventral lateral:			
Dorsal part	151.6 ± 13.7	139.8 ± 21.0	119.6 ± 15.3
Ventral part	101.8 ± 4.2	116.4 ± 20.1	85.6 ± 13.1
Caudal part	295.2 ± 23.4	142.4 ± 29.3	148.4 ± 25.7
Ventral posterolateral	272.8 ± 17.4	224.0 ± 32.1	193.0 ± 10.0
Ventral posteromedial	52.2 ± 5.9	36.0 ± 2.7	31.6 ± 4.1
Basal ventral medial	9.8 ± 2.0	9.2 ± 1.2	8.0 ± 1.5
Mediodorsal	602.2 ± 49.0	536.2 ± 48.6	443.0 ± 27.9
Parataenial	10.2 ± 1.0	6.7 ± 1.8	5.2 ± 0.8
Anterior paraventricular	40.8 ± 5.3	24.7 ± 7.9	37.4 ± 5.2
Paracentral	50.4 ± 7.5	54.2 ± 4.9	35.2 ± 3.2
Central medial	29.8 ± 5.3	28.2 ± 2.0	20.2 ± 3.5
Central lateral	27.6 ± 6.8	38.8 ± 7.5	31.4 ± 5.7
Centromedian	114.6 ± 10.9	103.2 ± 16.5	75.2 ± 5.8
Parafascicular	70.4 ± 4.0	73.0 ± 11.8	61.5 ± 4.9
Pulvinar:			
Anterior	70.6 ± 13.9	57.8 ± 12.3	72.2 ± 13.0
Lateral	354.8 ± 55.8	408.8 ± 38.9	262.2 ± 39.2
Medial	558.0 ± 59.6	572.4 ± 91.6	376.0 ± 25.5
Inferior (fibrous part)	38.4 ± 8.0	21.2 ± 9.3	21.4 ± 9.5
Inferior (cellular part)	30.0 ± 6.0	23.4 ± 6.3	22.4 ± 10.4
Reticular	535.6 ± 22.2	501.0 ± 27.1	372.4 ± 37.0*
Zona incerta	47.2 ± 7.4	32.4 ± 5.2	41.2 ± 2.2
Limitans/suprageniculate	65.0 ± 11.5	50.6 ± 2.7	36.8 ± 7.1
Subthalamus	90.2 ± 1.5	76.8 ± 7.1	67.4 ± 2.9
Whole thalamus	4429 ± 242	3982 ± 271	3225 ± 114*

* $P < 0.01$.

group (fig. 4) and it was restricted to the cases of AD ($P < 0.0001$). In 2 of these cases, no neurons at all could be identified (fig. 5). The other 3 cases had cell counts around 2000 which represents a neuronal loss of about 80% when compared with the control cases. In addition, over 50% of remaining neurons contained neurofibrillary tangles (fig. 6). There were also reductions in the mean nerve cell counts from the central medial nucleus (reduction of 37%) in the case of AD and from the anterior paraventricular (reduction of 58%) and anterior ventral lateral (external part only; reduction of 26%) nuclei in PD but none of these achieved statistical significance.

Another important finding arising from this part of the study is not actually apparent

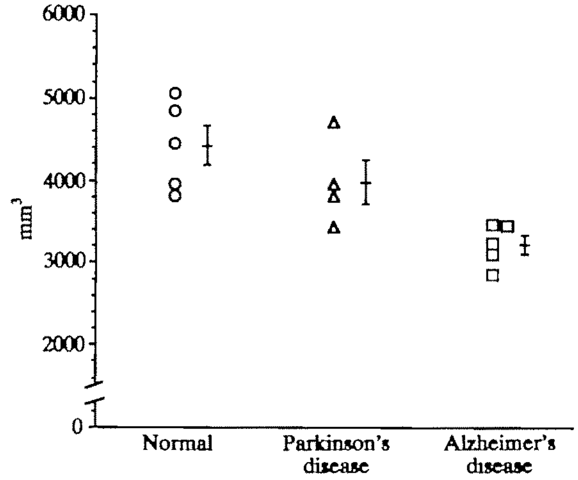

FIG. 2 Graph showing estimates of the total volume of dorsal thalamus ($\bar{x} \pm$ SEM) in controls, PD cases and AD cases. In 1 PD case the medial part of the rostral thalamus was not well covered on coronal tissue sections so that no volume measurements were possible on the parataenial, paraventricular and central medial nuclei or the thalamus as a whole. The difference between the mean volume of the dorsal thalamus in the AD group and the controls was statistically significant ($P < 0.01$).

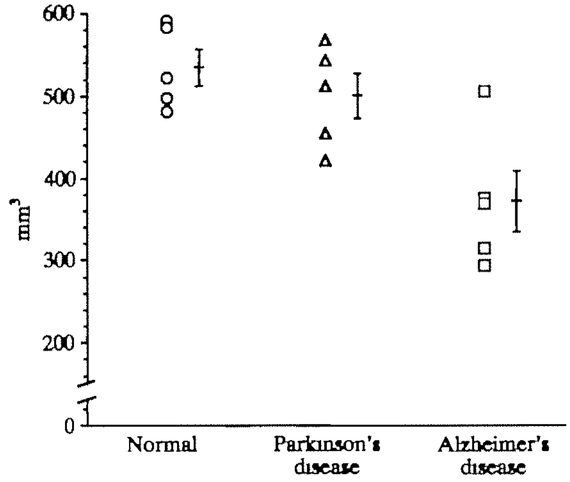

FIG 3. Graph showing estimates of the volume of the reticular nucleus of the thalamus ($\bar{x} \pm$ SEM) in controls, PD cases and AD cases. The difference between the mean volume of this nucleus in the AD group compared with the controls was statistically significant ($P < 0.01$).

in Table 3. It concerns the centromedian nucleus in which there is no significant difference between the mean nerve cell counts for the three groups. Nevertheless, for the centromedian nucleus, examination of Nissl-stained tissue sections did show neuronal degeneration and nerve cell loss in almost all cases. Indeed, only 2 PD cases showed no obvious histological abnormality of the centromedian nucleus. These cases had neuronal counts of 496 000 and 474 000, respectively (fig. 7). The healthy centromedian nucleus should therefore contain about half a million neurons. Given this reference, it is apparent that the majority of the elderly subjects examined had lost between 35% and 80% of the centromedian neurons. In contrast to the anterodorsal nucleus, the neuronal loss in the centromedian nucleus was not associated with any significant neurofibrillary tangle formation.

Fig. 8A shows a section of the centromedian nucleus from a 48-yr-old man who died

TABLE 3 NEURONAL COUNTS IN INDIVIDUAL THALAMIC NUCLEI AND IN THE SUBTHALAMIC NUCLEUS BASED ON SEMISERIAL PARAFFIN SECTIONS FROM 5 CONTROLS, 5 PD CASES AND 5 AD CASES

	Neuronal counts (×1000)		
Nucleus	*Normal (mean ± SEM)*	*Parkinson's disease (mean ± SEM)*	*Alzheimer's disease (mean ± SEM)*
Principal anterior	642.2 ± 45.8	631.6 ± 57.9	594.0 ± 52.2
Anterodorsal	11.9 ± 1.0	10.1 ± 1.9	1.1 ± 0.4*
Lateral dorsal	307.8 ± 27.2	244.0 ± 29.9	239.9 ± 33.6
Lateral posterior	570.6 ± 144	661.1 ± 137	842.0 ± 114
Ventral anterior	350.5 ± 65.7	324.8 ± 52.2	340.7 ± 43.8
Anterior ventral lateral.			
External part	659.6 ± 41.5	490.0 ± 18.6	529.6 ± 55.4
Internal part	434.6 ± 59.2	307.3 ± 67.7	327.3 ± 87.0
Principal ventral medial	71.3 ± 38.6	33.7 ± 11.4	23.5 ± 6.8
Posterior ventral lateral:			
Dorsal part	524.0 ± 26.8	491.0 ± 62.8	517.3 ± 70.5
Ventral part	303.3 ± 12.4	364.1 ± 51.6	320.0 ± 30.3
Caudal part	1232.0 ± 167	624.1 ± 161	745.0 ± 154
Ventral posterolateral	875.9 ± 55.8	699.0 ± 127	838.0 ± 75.7
Ventral posteromedial	301.9 ± 32.6	191.9 ± 26.7	220.4 ± 37.5
Basal ventral medial	76.0 ± 16.9	58.6 ± 9.5	57.0 ± 13.1
Mediodorsal	3916.0 ± 296	3308.0 ± 434	3078.0 ± 347
Parataenial	64.7 ± 4.5	43.8 ± 11.7	30.2 ± 4.2
Anterior paraventricular	508.7 ± 95.5	213.2 ± 40.1	313.3 ± 80.6
Paracentral	298.1 ± 44.0	317.2 ± 27.9	241.6 ± 14.4
Central medial	197.3 ± 29.5	209.4 ± 32.8	125.4 ± 20.8
Central lateral	203.4 ± 50.5	250.4 ± 53.5	291.1 ± 62.6
Centromedian	297.5 ± 17.1	297.8 ± 81.3	220.5 ± 39.4
Parafascicular	579.9 ± 37.1	525.8 ± 59.9	586.8 ± 63.7
Pulvinar:			
Anterior	367.5 ± 71.5	285.6 ± 56.8	473.7 ± 109
Lateral	1881.0 ± 225	1856.0 ± 291	1543.0 ± 80.1
Medial	3153.0 ± 333	3244.0 ± 501	2512.0 ± 213
Inferior (fibrous part)	191.0 ± 53.8	90.8 ± 40.1	158.9 ± 68.3
Inferior (cellular part)	217.4 ± 58.6	157.0 ± 44.8	181.0 ± 83.3
Reticular	1226.0 ± 72.8	1030.0 ± 93.0	917.8 ± 157
Zona incerta	267.4 ± 54.4	149.6 ± 31.0	254.1 ± 44.1
Limitans/suprageniculate	654.1 ± 76.7	492.8 ± 35.3	410.0 ± 78.2
Subthalamus	273.1 ± 18.4	261.7 ± 30.8	266.9 ± 25.1

* $P < 0.01$

from myocardial infarction and had no evidence of neurological illness. In comparison, fig. 8B shows the same nucleus from a case of AD. Loss of nerve cell bodies is evident. The great majority of those that remain are degenerate and reduced to irregular, dark, shrunken structures often lying along the margin of their residual lacunes within the neuropil (fig. 8C). An increased number of astrocytic nuclei is present. This neuronal degeneration was anatomically discrete in all cases. Fig. 8D shows it is limited to the centromedian nucleus while the adjacent mediodorsal nucleus is not involved. Similarly, nerve cells in the crescentic ventral posteromedial nucleus just external to the centromedian nucleus are spared.

A number of possible correlations were sought in order to determine the significance

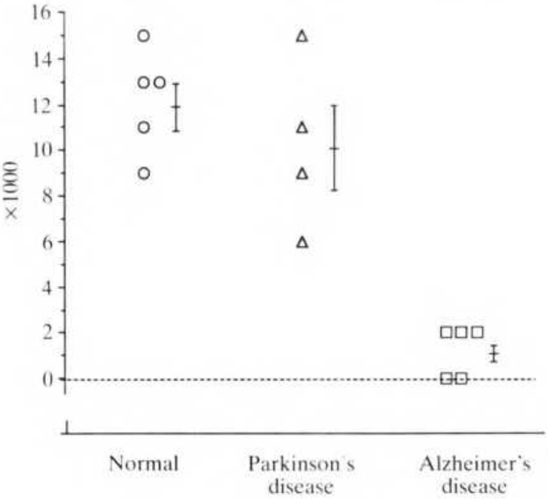

FIG. 4. Graph showing estimates of the total number of nerve cells in the anterodorsal nucleus of the thalamus ($\bar{x} \pm$ SEM) in controls, PD cases and AD cases. The difference between the mean neuronal count in the AD group and the controls was statistically significant ($P < 0.01$).

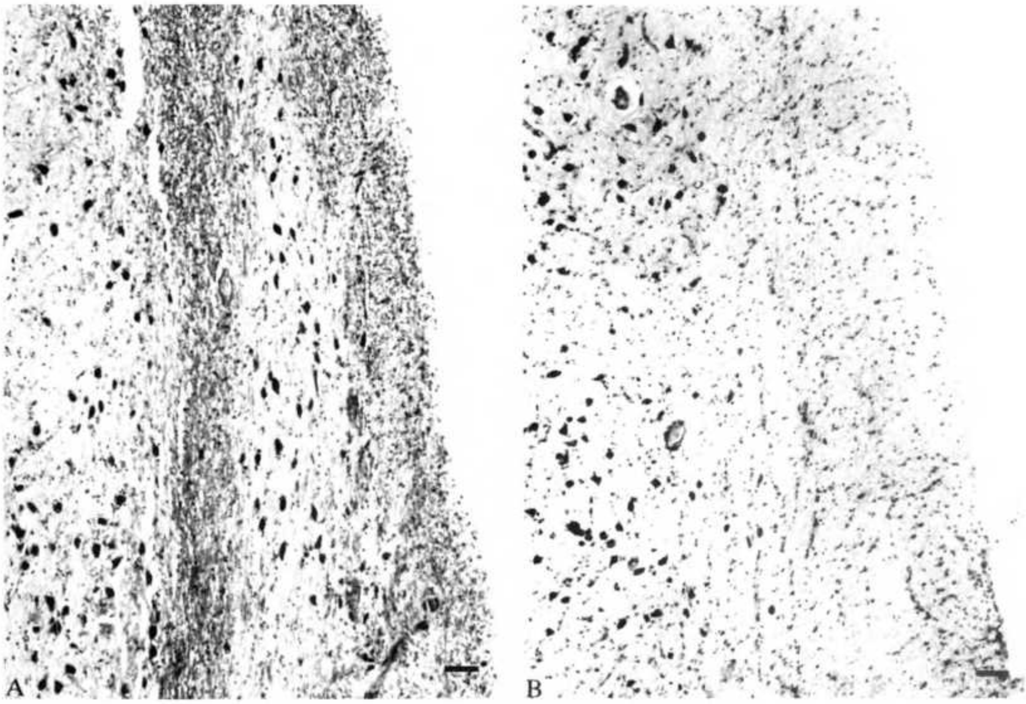

FIG. 5. A, photomicrograph of anterodorsal nucleus from elderly control. The anterodorsal nucleus is a thin lamina of cells curving round the large anteroventral nucleus at the left edge of the photograph. Combined Luxol fast blue and cresyl violet stain. Bar = 100 μm. B, photomicrograph of anterodorsal nucleus from a case of Alzheimer's disease. There is complete loss of nerve cell bodies from the anterodorsal nucleus. The anteroventral nucleus at the left edge of the photograph did not show any significant cell loss. Cresyl violet stain. Bar = 100 μm.

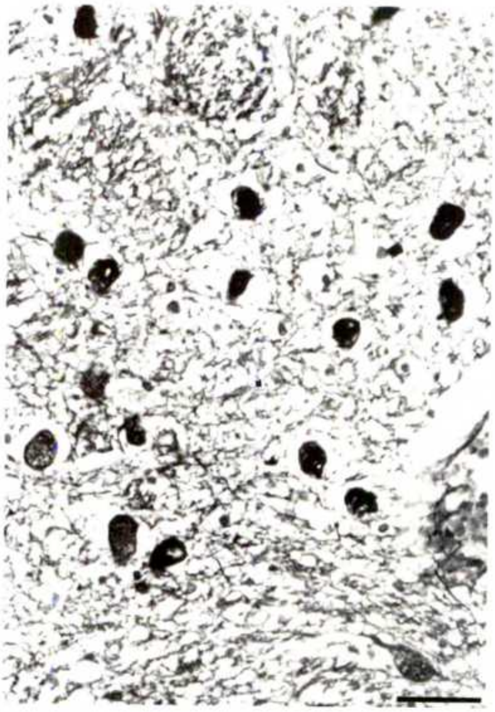

FIG. 6. Photomicrograph of anterodorsal nucleus from a case of Alzheimer's disease. Although neurons are still present in this nucleus, they show considerable degeneration with the formation of tightly wound, globose neurofibrillary tangles. Palmgren silver preparation. Bar = 50 μm.

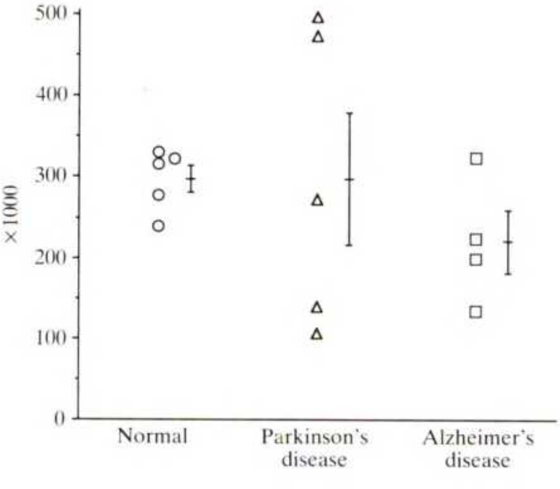

FIG. 7. Graph showing estimates of the total number of nerve cells in the centromedian nucleus of the thalamus ($\bar{x} \pm$ SEM) in controls, PD cases and AD cases. One case of AD had a small area of recent infarction involving the caudal intralaminar thalamic nuclei so that data were obtained from 4 cases in this group.

of the pathological changes in the centromedian nucleus. There was no significant correlation between centromedian neuronal counts and the presence and degree of cognitive impairment in life. It was not surprising, therefore, to discover no correlation between the neuritic plaque densities in the cerebral neocortex and the numbers of centromedian nerve cells. There was no evident correlation between the numbers of

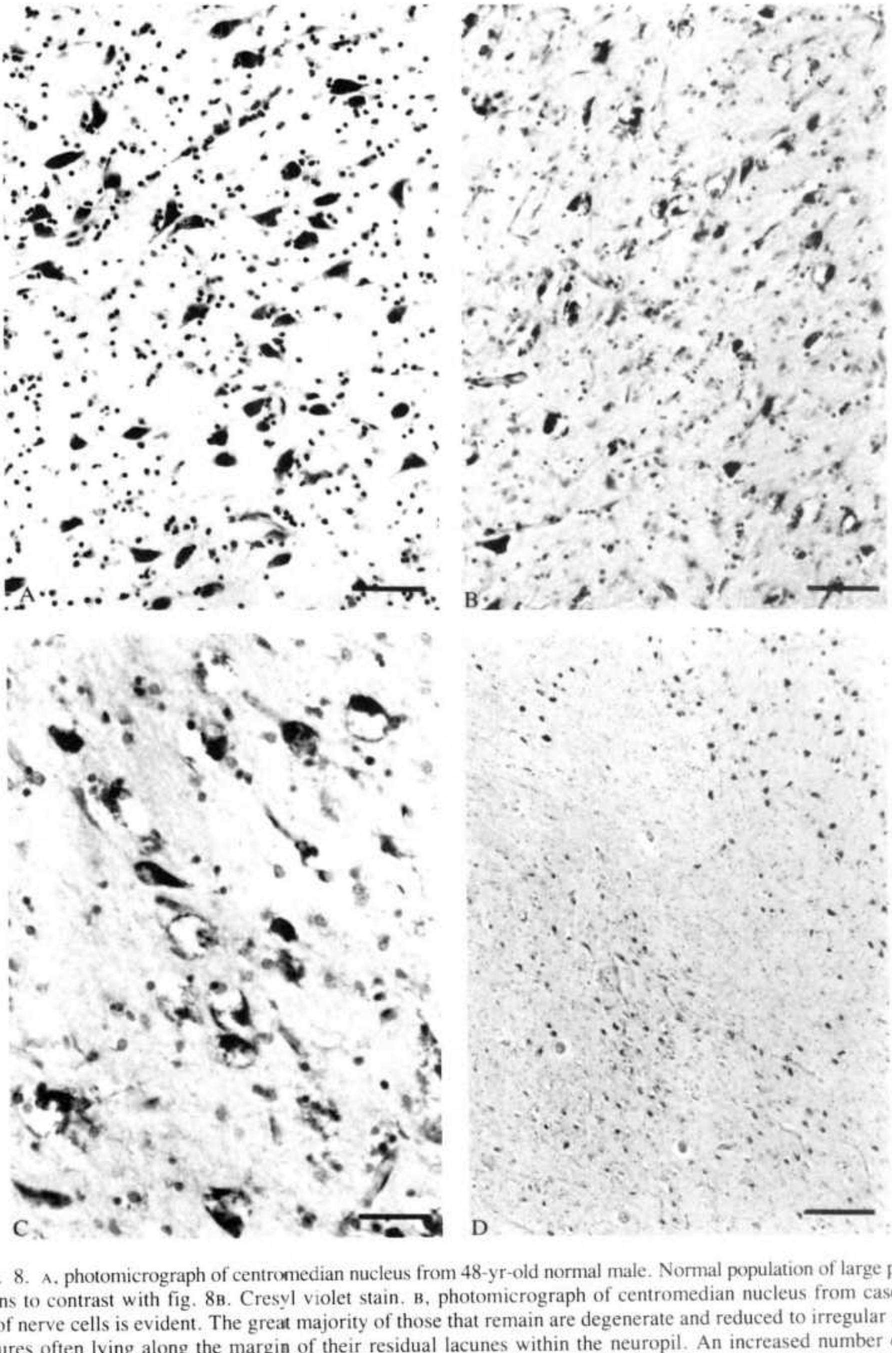

FIG. 8. A, photomicrograph of centromedian nucleus from 48-yr-old normal male. Normal population of large pyramidal neurons to contrast with fig. 8B. Cresyl violet stain. B, photomicrograph of centromedian nucleus from case of AD. Loss of nerve cells is evident. The great majority of those that remain are degenerate and reduced to irregular shrunken structures often lying along the margin of their residual lacunes within the neuropil. An increased number of lightly staining astrocytic nuclei are present. Cresyl violet stain. C, higher magnification photomicrograph of centromedian nucleus from same case as fig. 8B showing detail of neuronal disintegration and an increased number of astrocytic nuclei. Cresyl violet stain. D, photomicrograph of boundary between centromedian nucleus (at bottom left of picture) and mediodorsal nucleus (top right of picture) from a case of AD. The neuronal degeneration is sharply limited to the centromedian nucleus. Cresyl violet stain. Bars = 100 μm.

neurons in the centromedian nucleus and the ages of patients at death. Thus it would seem that within the context of the last 30 yrs of life there is no obvious progressive decline in the number of centromedian neurons with age.

Alzheimer-type pathology

Comment is restricted to the degree of neurofibrillary tangle formation in the anterior nuclear group and in the centromedian nucleus. A more detailed assessment of Alzheimer-type pathology in the thalamus is the subject of a separate report (Xuereb *et al.*, 1990).

DISCUSSION

This study of the thalamus in AD and PD has led to the discovery of three principal abnormalities. The first, a reduction in the total volume of the dorsal thalamus in AD, has probably only served to confirm what every neuropathologist already suspected. Nevertheless, such atrophy had neither been quantified nor proven statistically by direct comparison with data from a group of control cases. The second and most striking abnormality is the degree of neurofibrillary degeneration and nerve cell loss in the anterodorsal nucleus in AD. Thirdly, the variable and often severe nerve cell degeneration and loss in the centromedian nucleus that occurred in most brains, irrespective of whether they were from normal controls or from cases of PD or AD, returns this nucleus to the limelight after nearly half a century. One other point deserves emphasis. The very small samples used in this investigation limit its power to reveal differences between the groups. Only study of a much larger number of cases could determine whether any of the observed differences in neuronal counts that did not reach statistical significance may yet be meaningful.

Thalamic atrophy in Alzheimer's disease

The mean volume of the dorsal thalamus in the AD cases was 3225 mm^3. This amounted to a 27% reduction when compared with the mean thalamic volume of normal controls and the difference was found to be statistically significant. There was also a significant reduction in mean volume of the reticular nucleus in the AD group compared with controls, the reduction here amounting to 30%. The reticular nucleus consists of an outer lamina of nerve cells that form a concentric shell around the compact ovoid 'core' made up of the other individual dorsal thalamic nuclei. If this 'core' of thalamic nuclei atrophied as a whole, then the enveloping reticular nucleus would be expected to contract inwards. The reduction in the volume of the reticular nucleus may be interpreted as reflecting atrophy of the thalamus as a whole. In this latter regard, all the thalamic nuclei, except for the lateral posterior and central lateral nuclei, showed reductions in volume in AD even though these reductions did not individually achieve statistical significance.

The anterodorsal nucleus is the site of considerable pathological involvement in AD. It could not be identified at all in 2 cases and the other three cases showed an 80% loss of anterodorsal nerve cell bodies. This was the only part of the thalamus to show a significant loss of nerve cell bodies exclusive to AD. However, this loss of anterodorsal neurons could not possibly account for the overall reduction in the volume of the dorsal thalamus as it amounts to no more than a thin lamina of cells over the dorsomedial surface of the anterior tubercle. Without detracting from the possible significance of anterodorsal nucleus involvement in AD, it can be concluded that the observed reduction in volume of the thalamus is not accounted for by loss of nerve cell bodies from this, or indeed from any other individual nucleus. If cell loss cannot explain thalamic atrophy, then presumably such atrophy must be due either to loss of nerve cell processes (which include dendrites, axons and synaptic structures) or to changes in the glial cell population. It is possible that the thalamic atrophy in AD results from a reduction or loss of the large aggregation of synaptic terminals that characterize all the dorsal thalamic nuclei (Jones, 1985).

The anterodorsal nucleus in Alzheimer's disease

The anterior nuclear group is subdivided into anteroventral, anteromedial and anterodorsal nuclei. These are reciprocally connected with the limbic cortex of the cingulate gyrus, the retrosplenial area and the presubiculum and parasubiculum (Jones, 1985). The lateral dorsal nucleus is connected with the same parts of the cerebral cortex as the anterior nuclei (Ryszka and Heger, 1979; Robertson *et al.*, 1980). In AD, the hippocampal structures and amygdaloid nucleus are the earliest and most severely affected parts (Morel and Wildi, 1952; Jamada and Mehraein, 1968). It would therefore not be unreasonable to find any pathological changes that might occur in the thalamus in AD in those nuclei connected with the medial limbic portion of the temporal lobe.

This study has shown involvement of the anterior nucleus complex in AD. Surprisingly these changes were most striking and severe in the anterodorsal subdivision of this complex which in man consists only of a very thin lamina of cells curving round the dorsomedial surface of the large anteroventral nucleus. The principal anterior nucleus (anteroventral and anteromedial divisions) and the lateral dorsal nucleus did not show any evidence of nerve cell loss. Neurofibrillary tangles were present in an average of 2.6% of neurons in the principal anterior nucleus and in 8.3% of nerve cells in the lateral dorsal nucleus. Clearly the degree of neurofibrillary change in these latter nuclei was considerably less severe than in the anterodorsal division and was comparable with the degree of tangle formation seen in some other thalamic nuclei that have altogether different cortical connections (Xuereb *et al.*, 1990).

The combination of marked neurofibrillary tangle formation and severe cell loss occurring exclusively in the AD cases suggests that the anterodorsal nucleus is the site of 'primary' damage to nerve cells locally by the AD process. There is no clear explanation for the selective involvement of this particular division of the anterior nuclear complex. Experiments in the cat and rat (Kaitz and Robertson, 1981; Robertson and Kaitz, 1981) indicated that the anterodorsal nucleus has major connections with the retrosplenial limbic area while the anteroventral and lateral dorsal nuclei are principally connected with the cingulate area proper. The severity of Alzheimer-type pathology is greater in the retrosplenial area than in the posterior cingulate cortex and the anterior cingulate gyrus is relatively spared until late in AD (Brun, 1983). One might speculate, then, that the predominant anatomical connections between the anterodorsal nucleus and the retrosplenial limbic area may reflect some other common factor that predisposes each to the ravages of AD.

The anatomical or chemical basis for the relatively severe lesion in the anterodorsal nucleus and its possible clinical and behavioural consequences are entirely uncertain. Nevertheless, the changes in the anterodorsal nucleus could possibly prove helpful in the pathological diagnosis of AD. The quantification of neocortical plaque density based on a number of cortical areas is widely used as a means of assessing the severity of AD, and of distinguishing AD from the cerebral changes of normal ageing. This latter distinction is not difficult if there are numerous neurofibrillary tangles in the neocortex, that is outside the hippocampus and related entorhinal and parahippocampal regions. However, autopsy situations are often more difficult, since the clinical impression of dementia may have been much less certain or alternatively, tangles may be absent from sections of neocortex. The diagnosis of AD then becomes a matter of quantitative distinction and leaves room for error and controversy. It may be that severe cell loss and neurofibrillary tangle formation in the anterodorsal nucleus could prove to be as striking a marker of AD as is the combination of numerous plaques and tangles in the neocortex.

Neuronal degeneration in the centromedian nucleus

Neuronal degeneration and loss in the centromedian nucleus were equally severe in elderly controls and in both disease groups indicating that the changes in this nucleus could not possibly be directly or solely related to either the PD or AD processes. This is confirmed by the lack of neurofibrillary tangles in the centromedian nucleus in AD, in marked contrast to the findings in the anterodorsal nucleus.

The possibility has to be considered that the neuronal changes are simply histological artefact in some way related to fixation or processing of tissue. There are two reasons why this is unlikely. First, the neuronal degeneration is anatomically discrete. In every case in which it was present the changes were sharply limited to the centromedian nucleus and did not involve the adjacent mediodorsal, ventral posteromedial or even the parafascicular nuclei. Secondly, and more emphatically, neuronal loss was associated with a proportionate increase in the number of astrocytes. Such a glial reaction indicates antemortem neural damage.

The next question that arises is whether the histological alterations in the centromedian nucleus are a secondary phenomenon. They could theoretically represent either retrograde changes occurring in nerve cells due to interruption of efferent fibres from the centromedian nucleus or transneuronal (anterograde) atrophy due to interruption of afferent fibres to the nucleus. Whilst the microscopic appearances of acute retrograde degeneration are characteristic (Nissl, 1892), there are no specific histological features that distinguish between anterograde and retrograde neuronal changes in chronic neurological disease. It is more useful to consider the fibre connections of the centromedian nucleus (Carpenter and Sutin, 1983). Together with the other intralaminar nuclei it projects heavily to the striatum. The internal segment of the globus pallidus reciprocates with a heavy projection to the centromedian nucleus. In addition, this nucleus connects with the motor and parietal cortex and receives a cholinergic projection from the pontomesencephalic tegmentum (Sugimoto and Hattori, 1984).

None of the cases in this study had significant pathology of the striopallidal complex so that the centromedian changes cannot be regarded as secondary to lesions at this site. The amount of cortical Alzheimer-type pathology was assessed semiquantitatively in each case and a statistical correlation was sought between centromedian neuronal counts and neocortical plaque densities. No such correlation was found. This was of course not unexpected, as the normal control cases had no cortical pathology and yet had just as severe neuronal loss in centromedian nucleus as the cases in the PD and AD groups. It would therefore appear unlikely that the observed changes in centromedian nucleus occurred secondary to pathology in the cerebral cortex.

The third possible consideration is that lesions of the hindbrain cholinergic tegmental nuclei led to anterograde degeneration of centromedian nerve cells. Unfortunately, no assessment of the pontomesencephalic nuclei of these cases was possible. Nevertheless, it is not unreasonable to presume that if these hindbrain cholinergic nuclei were primarily responsible then secondary changes should be found in the anterior thalamic nucleus, the subthalamic nucleus and the globus pallidus which are the other principal targets of the hindbrain cholinergic projections (Sugimoto and Hattori, 1984; Sofroniew *et al.*, 1985). No evidence of nerve cell loss (except for the specific changes in the anterodorsal division of the anterior nucleus already referred to above) was found and this fact alone must argue considerably against this possibility.

Having discounted these possibilities, the more plausible conclusion remains that the nerve cell degeneration and loss in the centromedian nucleus is a primary phenomenon and may reflect a peculiar susceptibility of centromedian neurons to age involution. This was precisely the conclusion drawn by Vogt and Vogt (1941) when they first discovered similar changes in the centromedian nucleus. Clearly a detailed quantitative study of the centromedian nucleus in young, middle-aged and elderly individuals with no neurological illness is required as a first step towards a better understanding of age-related cell loss from this nucleus.

REFERENCES

American Psychiatric Association (1980) *DSM-III: Diagnostic and Statistical Manual of Mental Disorders*. Third edition. Washington, DC: American Psychiatric Association.

Andrew J, Watkins ES (1969) *A Stereotaxic Atlas of the Human Thalamus and Adjacent Structures: a Variability Study*. Baltimore: Williams and Wilkins.

Arendt T, Bigl V, Arendt A, Tennstedt A (1983) Loss of neurons in the nucleus basalis of Meynert in Alzheimer's disease, paralysis agitans and Korsakoff's disease. *Acta Neuropathologica, Berlin*, **61**, 101–108.

Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry*, **114**, 797–811.

Bondareff W, Mountjoy CQ, Roth M (1982) Loss of neurons of origin of the adrenergic projection to cerebral cortex (nucleus locus ceruleus) in senile dementia. *Neurology, New York*, **32**, 164–168.

Braunmühl A von (1928) Zur Histopathologie der umschriebenen Grosshirnrindenatrophie (Pickche Krankheit). *Virchow's Archiv fur Pathologische Anatomie und Physiologie und für Klinische Medizin*, **270**, 448–486.

Braunmühl A von (1931) Neue Gesichtspunkte zum Problem der Senilen Plaques. *Zeitschrift für die Gesamte Neurologie und Psychiatrie*, **133**, 391–441.

Brun A (1983) An overview of light and electron microscopic changes. In: *Alzheimer's Disease*. Edited by B. Reisberg. New York: Free Press, pp. 37–47.

Candy JM, Perry RH, Perry EK, Irving D, Blessed G, Fairbairn AF *et al.* (1983) Pathological changes in the nucleus of Meynert in Alzheimer's and Parkinson's diseases. *Journal of the Neurological Sciences*, **59**, 277–289.

Carpenter MB, Sutin J (1983) *Human Neuroanatomy*. Eighth edition. Baltimore: Williams and Wilkins.

CROSS RB (1982) Demonstration of neurofibrillary tangles in paraffin sections: a quick and simple method using a modification of Palmgren's method. *Medical Laboratory Sciences*, **39**, 67–69.

ESCOUROLLE R, DE RECONDO J, GRAY F (1971) Etude anatomo-pathologique des syndromes parkinsoniens. In: *Monoamines Noyaux Gris Centraux et Syndrome de Parkinson*. Edited by J. de Ajuriaguerra and G. Gauthier. Geneva: Georg-Masson, pp. 173–229.

FORNO LS (1978) The locus ceruleus in Alzheimer's disease. *Journal of Neuropathology and Experimental Neurology*, **37**, 614.

HASSLER R, MUNDINGER F, RIECHERT T (1979) *Stereotaxis in Parkinson Syndrome: Clinical-Anatomical Contributions to its Pathophysiology with an Atlas of the Basal Ganglia in Parkinsonism*. Berlin: Springer.

ISHII T (1966) Distribution of Alzheimer's neurofibrillary changes in the brain stem and hypothalamus of senile dementia. *Acta Neuropathologica, Berlin*, **6**, 181–187.

JAMADA M, MEHRAEIN P (1968) Verteilungsmuster der senilen Veränderungen im Gehirn: Die Beteiligung des limbischen Systems bei hirnatrophischen Prozessen des Seniums und bei Morbus Alzheimer. *Archiv für Psychiatrie und Nervenkrankheiten*, **211**, 308–324.

JELLINGER K (1987) The pathology of parkinsonism. In: *Movement Disorders 2*. Edited by C. D. Marsden and S. Fahn. London: Butterworths, p. 145.

JONES EG (1985) *The Thalamus*. New York: Plenum Press.

KAITZ SS, ROBERTSON RT (1981) Thalamic connections with limbic cortex. II. Corticothalamic projections. *Journal of Comparative Neurology*, **195**, 527–545.

KLÜVER H, BARRERA E (1953) A method for the combined staining of cells and fibers in the nervous system. *Journal of Neuropathology and Experimental Neurology*, **12**, 400–403.

MANN DMA, LINCOLN J, YATES PO, STAMP JE, TOPER S (1980) Changes in the monoamine containing neurones of the human CNS in senile dementia. *British Journal of Psychiatry*, **136**, 533–541.

MANN DMA, YATES PO, HAWKES J (1983) The pathology of the human locus ceruleus. *Clinical Neuropathology*, **2**, 1–7.

MOREL F, WILDI E (1952) General and cellular pathochemistry of senile and presenile alterations of the brain. In: *Proceedings of the First International Congress of Neuropathology, Turin*. Rome: Rosenberg and Sellier, 2, pp. 347–374.

NIEUWENHUYS R (1985) *Chemoarchitecture of the Brain*. Berlin: Springer, p. 124.

NISSL F (1892) Über die Veränderungen der Ganglienzellen am Facialiskern des Kaninchens nach Ausreissung der Nerven. *Allgemeine Zeitschrift für Psychiatrie*, **48**, 197–198.

OPPENHEIMER DR (1984) Diseases of the basal ganglia, cerebellum and motor neurons. In: *Greenfield's Neuropathology*. Fourth edition. Edited by J. H. Adams and J. A. N. Corsellis and L. W. Duchen. London: Edward Arnold, pp. 699–747.

ROBERTSON RT, KAITZ SS, ROBARDS MJ (1980) A subcortical pathway links sensory and limbic systems of the forebrain. *Neuroscience Letters*, **17**, 161–165.

ROBERTSON RT, KAITZ SS (1981) Thalamic connections with limbic cortex. I. Thalamocortical projections. *Journal of Comparative Neurology*, **195**, 501–525.

RYSZKA A, HEGER M (1979) Afferent connections of the laterodorsal thalamic nucleus in the rat. *Neuroscience Letters*, **15**, 61–64.

SIMMA K (1949) Das Centrum medianum thalami im Greisenalter und bei seniler Demenz. *Monatsschrift für Psychiatrie und Neurologie*, **118**, 44–60.

SIMMA K (1951) Über Thalamusveränderungen bei Seniler Demenz und bei der Alzheimerschen Krankheit. *Monatsschrift für Psychiatrie und Neurologie*, **122**, 156–178.

SOFRONIEW MV, PRIESTLEY JV, CONSOLAZIONE A, ECKENSTEIN F, CUELLO AC (1985) Cholinergic projections from the midbrain and pons to the thalamus in the rat, identified by combined retrograde tracing and choline acetyltransferase immunohistochemistry. *Brain Research, Amsterdam*, **329**, 213–223.

SUGIMOTO T, HATTORI T (1984) Organization and efferent projections of nucleus tegmenti pedunculopontinus pars compacta with special reference to its cholinergic aspects. *Neuroscience*, **11**, 931–946.

TOMLINSON BE, BLESSED G, ROTH M (1968) Observations on the brains of non-demented old people. *Journal of the Neurological Sciences*, **7**, 331–356.

TOMLINSON BE, BLESSED G, ROTH M (1970) Observations on the brains of demented old people. *Journal of the Neurological Sciences*, **11**, 205–242.

TOMLINSON BE, IRVING D, BLESSED G (1981) Cell loss in the locus coeruleus in senile dementia of Alzheimer type. *Journal of the Neurological Sciences*, **49**, 419–428.

TOMLINSON BE, CORSELLIS JAN (1984) Ageing and the dementias. In: *Greenfield's Neuropathology*. Fourth edition. Edited by J. H. Adams, J. A. N. Corsellis and L. W. Duchen. London: Edward Arnold, pp. 951–1025.

VOGT C, VOGT O (1941) Thalamusstudien I–III: I. Zur Einführung II. Homogenität und Grenzgestaltung der Grisea des Thalamus. III. Das Griseum centrale (Centrum medianum Luys). *Journal für Psychologie und Neurologie*, **50**, 32–154.

WHITEHOUSE PJ, PRICE DL, CLARK AW, COYLE JT, DELONG MR (1981) Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis *Annals of Neurology*, **10**, 122–126.

WHITEHOUSE PJ, HEDREEN JC, WHITE CL, PRICE DL (1983) Basal forebrain neurons in the dementia of Parkinson disease. *Annals of Neurology*, **13**, 243–248.

XUEREB JH, CANDY JM, PERRY EK, PERRY RH, MARSHALL E, BONHAM JR (1990) Distribution of neurofibrillary tangle formation and [^{3}H]-D-aspartate receptor binding in the thalamus in the normal elderly brain, in Alzheimer's disease and in Parkinson's disease. *Neuropathology and Applied Neurobiology*, **16**, 477–488.

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SYMPATHETIC SKIN RESPONSE IN PATIENTS WITH MULTIPLE SCLEROSIS COMPARED WITH PATIENTS WITH SPINAL CORD TRANSECTION AND NORMAL CONTROLS

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SUMMARY

In 28 patients with definite multiple sclerosis (MS) and 21 patients with a functionally complete transection of the spinal cord sympathetic skin responses (SSR) from both the palms and soles were studied. In the patients with a complete transection at T3 or 4, SSRs were impaired in the palms as well as the soles, and most patients with a transection at T11 or T12 had normal SSRs in the soles. These findings indicate that the central pathway mediating the SSR descends to the upper thoracic cord where connections are made with the sympathetic distribution to the palms, and then to the lower thoracic cord to reach the sympathetic outflow to the soles. This is compatible with the anatomical knowledge of the sympathetic system. Of the MS patients, 75% had abnormal SSR results. The SSR for the soles was more sensitive than that for the palms. The incidence of SSR abnormality was as high as those of somatosensory evoked potential (SEP) (79%) and visual evoked potential (VEP) (75%) abnormalities. Of the patients with normal SEPs 14% had impaired SSRs and 21% had abnormal SSR with normal VEPs. When the results of these 3 tests were combined, the abnormality increased to 100%.

From our study, the SSR probably reflects not only postganglionic sympathetic activity but also preganglionic function. The SSR is therefore useful in evaluating myelopathy, providing information different from that given by assessment of the somatic nervous system. Since the SSR detected a few MS lesions which were not demonstrated by other evoked potentials, it is potentially a new tool for the detection of MS lesions in addition to conventional evoked potential studies.

INTRODUCTION

Since Féré, a French clinician, discovered the decrease in skin resistance caused by pain in 1888, this phenomenon has been studied under the name of the 'galvanic skin response' (GSR). A change in skin resistance occurs after emotional stimuli and is used as an indicator of emotional change in psychological studies. This is probably due to the movement of ions across the membrane of sweat gland cells in the skin and reflects sudomotor activity (Wang, 1957). Based on the GSR, Shahani *et al.* (1984) recently described a technique known as the 'sympathetic skin response' (SSR). This test demonstrates a change in the voltage measured from the surface of the skin after electrical

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stimulation of peripheral nerve afferents or deep inspiration, and is also attributed to sudomotor activity. The final efferent pathway of SSR is considered to pass through unmyelinated postganglionic sympathetic fibres because the SSR is synchronized with sympathetic skin activity on microneurography (Hagbarth *et al.*, 1972) and is blocked by the iontophoresis of atropine or by sympathectomy (Knezevic and Bajada, 1985). On this basis, the SSR has come to be used for evaluating postganglionic sympathetic activity in clinical neurology as no conventional electrophysiological procedure is available to assess to the autonomic nervous system adequately. Especially in diabetic neuropathy, the SSR has been considered to be a valuable test for the investigation of sympathetic dysfunction (Knezevic and Bajada, 1985; Soliven *et al.*, 1987; Watahiki, 1988; Niakan and Harati, 1988; Maselli *et al.*, 1989).

Although the afferent pathway of the SSR is considered to involve large myelinated sensory fibres, little is known about the central pathway of SSR. However, it is presumed to ascend rostrally to the brainstem, since the SSR is closely related to consciousness. Furthermore, in animal experiments, the GSR was elicited by electrical stimulation of the sensorimotor area in cerebral cortex and the hypothalamus (Wang and Richter, 1928; Langworthy and Richter, 1930; Wang and Lu, 1930). Wang *et al.* (1956*a*, *b*) showed that the reticular system in the brainstem plays a role in the maintenance of the GSR. The SSR is therefore expected to be useful for evaluating myelopathy and brainstem dysfunction as well as peripheral neuropathy. The present paper has the two following aims. First, as a positive control for myelopathy, the SSR was studied in patients with myelopathy due to spinal injury, vascular lesions or tumours, the sites of which were clearly documented. Secondly, in 28 patients with multiple sclerosis, the SSR was studied and its value for assessing the integrity of the long tracts in this disease was investigated in comparison with the results of somatosensory (SEP) and visual evoked potentials (VEP).

SUBJECTS

The SSR was obtained in 28 patients with multiple sclerosis (MS) (6 males and 22 females, age range 18–71 yrs, mean age 43.6 yrs). They were diagnosed as clinically definite MS by Poser's criteria (1983). All MS patients were studied with magnetic resonance imaging (MRI). Seventeen patients had optic neuritis and transverse myelopathy, 4 had recurrent brainstem symptoms with multiple lesions in the brainstem; 3 had recurrent symptoms in the brainstem and spinal cord; 4 had recurrent transverse myelopathy with multiple lesions in the spinal cord and 9 had several small lesions in cerebral white matter on MRI.

In addition to 50 normal controls (age range 18–75 yrs, mean age 44.6 yrs), 21 patients with a functionally complete transection of the spinal cord (17 with spinal cord injury and 4 with spinal vascular lesions, age range 20–26 yrs, mean age 32.3 yrs) and 12 patients with a functionally incomplete transection of the spinal cord (7 with spinal cord injury and 5 with spinal tumours, age range 21–75 yrs, mean age 40.5 yrs) were studied as positive controls for myelopathy. The patients with a functionally complete transection of the spinal cord had lost all voluntary motor function and sensation below the level. Table 2 shows the level of the lesion of patients with complete transection of the spinal cord and 1 with the Brown-Séquard syndrome (Case K). Case K had evidence of complete transection in the right side of the cord, i.e., a complete loss of motor function in the right leg and of sensation below the level of T4 on the left side.

METHODS

For SSR recordings, the relaxed patient lay on a couch in a warm, quiet room. The patient was asked to keep his/her eyes open and not to fall asleep. Standard electromyographic disc electrodes were covered with conducting paste and attached to the palm (G1) and dorsum of the hand (G2) as well as to the sole (G1) and dorsum of the foot (G2) bilaterally. Recordings were obtained on a Nihon Koden polygraphic EEG-4214, with a frequency response from 0.53 to 1000 Hz. Stimuli consisted of single square pulses of 200 μs duration, 50–150 V intensity, applied to the supraorbital nerves bilaterally on the forehead. More than 10 electrical stimuli were administered at irregular intervals greater than 30 s apart. The skin temperature in all patients was kept above 31° C. The latency and peak-to-peak amplitude of each response were measured, and the response with largest amplitude and that with the shortest latency were selected. The ratio of amplitudes of left and right responses in palms and soles, and that of ipsilateral palm and sole in the largest response, were calculated. The left-right ratio was the result of the amplitude of the smaller of the left and right responses divided by that of the larger one.

In addition to the SSR, SEPs and VEPs were studied in MS patients using a Nihon-Koden Neuropack 8 SEPs were obtained by stimulation of the median nerve at the wrist and the tibial nerve at the ankle. The stimulus strength was adjusted to 10–20% above the motor threshold of the thenar and plantar muscles at a rate of 5/s. Recordings for the median nerve were made from Erb's point ipsilaterally, the second cervical vertebral spinous process and the contralateral parietal scalp and referenced at Fz (10-20 International System). Recordings for the tibial nerve were made over the twelfth thoracic vertebral spinous process (T12) and referenced to a site 5 cm rostral to T12, and from a site 2 cm posterior to the vertex at the midline and referenced to Fz. The findings were considered to be abnormal when the cortical responses or N13 (the negative peak from the cervical electrode) disappeared, and the interpeak latency of N13-N20 in median nerve SEP and that of N20(T12)-P40 in tibial nerve SEP (central conduction time) were greater than 6.8 and 24.6 ms, respectively, which are 3 SDs above the mean for 20 normal controls.

VEPs were recorded at a stimulus rate of 2/s. Pattern reversal was produced by a rapid lateral displacement of the checkerboard through one square and the subject sat 1 m in front of the screen. The whole stimulating field was subtended 1.3° at the eye. A recording electrode was placed at Oz and a reference electrode was placed at Fz. The finding was abnormal if P100 latencies were greater than 107.8 ms, which is 3 SDs above the normal average.

RESULTS

SSRs were obtained in all controls at the palms and soles after electrical stimulation. The SSR consisted of biphasic or triphasic potential usually with a negative and sometimes a positive initial peak. The amplitude of response varied between and within subjects from test to test, with a tendency to diminish in amplitude with repeated stimulation. Occasionally the responses completely disappeared from habituation. When the responses habituated, all responses in both the palms and soles disappeared simultaneously; there was no instance in which responses at some sites disappeared while responses in other sites were consistently recorded. The waveform of the response sometimes changed markedly during the tests. Table 1 shows the shortest latencies and largest amplitudes of SSRs, and the ratio of left-right, palm/sole amplitudes in the largest response after the electrical stimulation in normal controls. The SSR latency was always more prolonged when recorded at the sole than at the palm. The SSR amplitude varied greatly among the controls. It was difficult to be certain that a response was definitely reduced from the amplitude alone or from the sole/palm amplitude ratio because of their great variability in normal controls. The left-right ratio of amplitudes in palms or soles in normal controls, however, was relatively constant. There was no difference in the responses between sides either for amplitude or latency related to cerebral dominance.

Table 2 shows the results of SSRs in patients with complete transection of the spinal cord. In 6 out of 8 patients with cervical cord lesions (Cases B–D and F–H), no response was elicited either in the palms or soles. However, the remaining 2 patients (Cases A and E) had minimal but constant responses only in the palms on electrical stimulation

TABLE 1. SSR RESULTS OF NORMAL CONTROLS

	Amplitude (mV)	*Latency (s)*
L palm	5.63±3.26 (0.96−12.61)	1.34±0.10
R palm	5.53±3.24 (1.10−11.21)	1.34±0.10
L sole	1.71±1.12 (0.42−6.34)	1.83±0.26
R sole	1.64±1.08 (0.36−6.96)	1.84±0.28

Left-right ratio of amplitudes in palms	81.8±10.3%
Left-right ratio of amplitudes in soles:	81.6±11.5%
Sole/palm ratio of amplitude:	32.9±14.8%

TABLE 2 SSR RESULTS IN PATIENTS WITH COMPLETE TRANSECTION OF SPINAL CORD

Case	*Lesion*	*Palm* *L/R*	*Sole* *L/R*
A	C5	+/+	−/−
B	C6	−/−	−/−
C	C6	−/−	−/−
D	C7	−/−	−/−
E	C7	+/+	−/−
F	C7	−/−	−/−
G	C8	−/−	−/−
H	C8	−/−	−/−
I	T3	−/−	−/−
J	T4	−/−	−/−
*K	RT4	N/↓	−/−
L	T6	N/↓	−/−
M	T8	N/N	−/−
N	T9	N/N	−/−
O	T10	N/N	−/−
P	T10	N/N	−/−
*Q	T11	N/N	N/N
*R	T12	N/N	−/−
S	T12	N/N	N/N
T	T12	N/N	N/N
*U	T12	N/N	N/N

* Patients with spinal vascular lesion. Other patients had spinal cord injury, − = no response; ↓ = asymmetric response, + = small response; C = cervical cord, T, thoracic cord; N = normal response

and deep inspiration, the amplitudes of which were less than 100 μV and were much smaller than normal. In 4 patients with the lesion at T3−6 (Cases I−L), not only did the plantar responses disappear, but palmar responses were disturbed (fig. 1) while motor and sensory functions were preserved in the upper limbs. In Case K with a Brown-Séquard syndrome due to a lesion at T4 level on the right, the amplitude of the SSR in the right palm was one-eighth of that on the left (fig. 2). In 4 patients with the lesion at T8−10 (Cases M−P), responses obtained at the palms were normal, but were absent in the soles. In 4 out of 5 patients with a lesion at T11 and 12 (Cases Q−U), responses were obtained in the soles as well as in the palms (fig. 3) despite complete deterioration of motor and sensory function in the legs. No patient had a response with a prolonged latency.

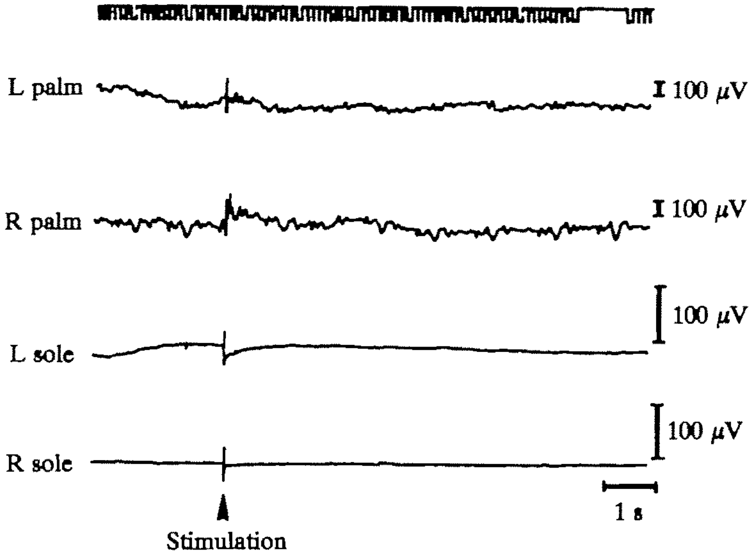

FIG. 1 SSR after electrical stimulation of the supraorbital nerves in *Case J* with complete transection at T4 level.

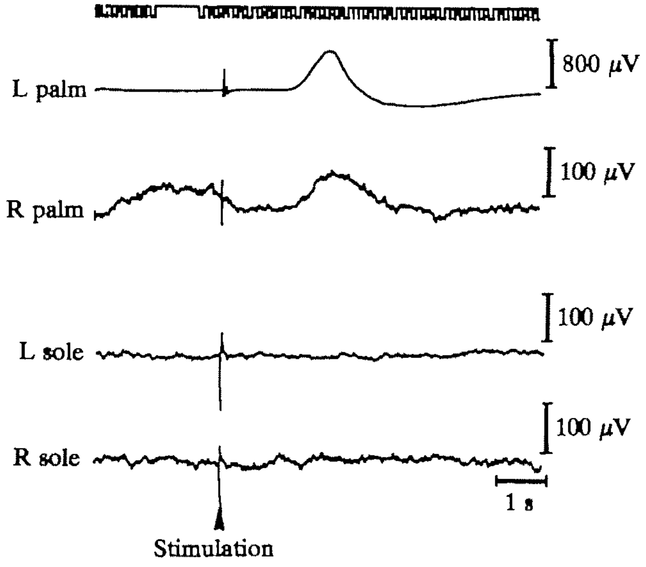

FIG. 2 SSR after electrical stimulation of the supraorbital nerves in *Case K* with a Brown-Séquard syndrome due to a right T4 lesion

In 3 patients with a functionally incomplete transection of the spinal cord at C2, C6 and T6, the responses in the soles sometimes disappeared while those in palms were consistently recorded (fig. 4).

Considering the SSR results in positive and negative controls, the following responses

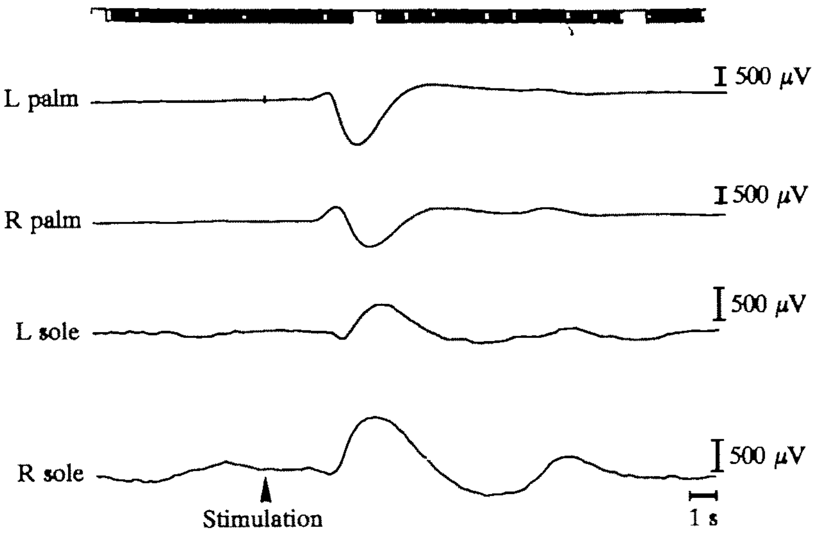

FIG 3 SSR after electrical stimulation of the supraorbital nerves in *Case S* with complete transection at T12 level

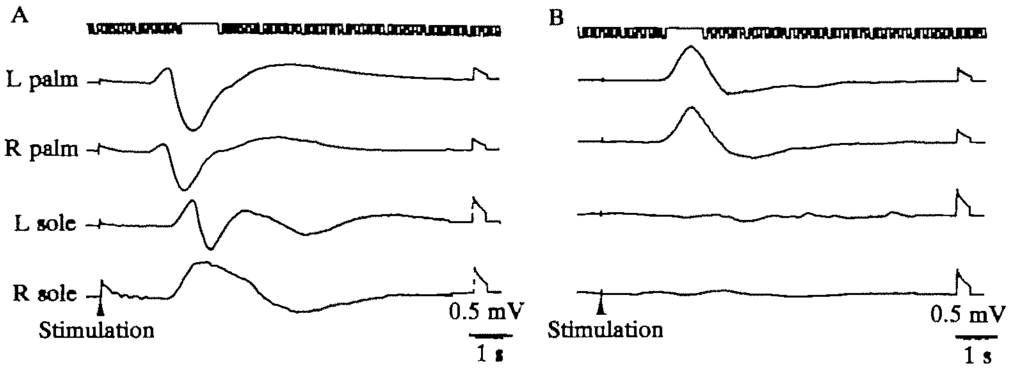

FIG. 4. SSRs in patients with incomplete transection at T8 due to spinal tumour. Fifth (A) and sixth (B) responses to 10 successive stimuli. The plantar responses sometimes disappeared (B) while palmar responses were consistently recorded (A).

are thought to be abnormal: (1) absence of response; (2) the responses in one site were sometimes absent while those in the other sites were constantly recorded (unstable response). In addition, we consider it an important finding when the amplitude of the response is less than 50% of that on the contralateral side (asymmetric response).

Table 3 shows the P100 latencies of VEPs and the central conduction times of SEPs in 28 patients with MS. In addition, Table 4 shows the sites of lesions and a summary of the VEP, SEP and SSR results. The sites of the lesions were evaluated by neurological symptoms and MRI results. Twenty-one patients (75.0%) showed abnormal SSR results. Abnormalities in the soles were observed in 20 patients, and the types of the abnormality

TABLE 3. THE RESULTS OF P100 LATENCIES OF VEPS AND CENTRAL CONDUCTION TIMES OF SEPs (MS)

Case	*VEPs R/L (P100)*	*SEPs*		*Case*	*VEPs R/L (P100)*	*SEPs*	
		RM/LM (N13–N20)	*RT/LT (N21–P40)*			*RM/LM (N13–N20)*	*RT/LT (N21–P40)*
1	134/129	–/7 9	25.8/36.0	15	92/89	5 4/5.7	–/–
2	121/138	6.6/6 3	19.7/22 0	16	130/117	5 4/5.6	14.1/17 9
3	104/142	6.0/9.9	18.8/35.6	17	–/87	5.4/5.8	14 7/15 5
4	112/–	*/*	–/–	18	121/120	4.9/5.2	26 5/27 8
5	86/83	7 5/6 6	26 6/18.0	19	99/–	5.6/5.8	24 7/19.4
6	153/–	–/8 6	21 1/28 6	20	118/–	5.9/6.0	–/–
7	99/104	7.0/7 4	24 0/35 9	21	92/94	5 8/5.8	–/–
8	130/132	6 0/5.8	18 4/19 0	22	129/107	6 3/6.5	20 2/25.5
9	–/88	6 4/6 2	19 1/19.0	23	126/132	5 6/4.7	–/–
10	112/138	7.2/5.6	26 8/18.8	24	95/97	5 6/5.8	–/–
11	100/130	6.2/12.4	–/–	25	87/86	5.6/5 9	20.0/21.2
12	–/–	6.2/–	43 8/38 0	26	107/107	5.6/5.8	22.4/20 8
13	129/145	–/6.2	–/–	27	–/104	5.9/5.9	15 0/–
14	94/92	5 9/5 5	18.1/17 5	28	120/–	5 6/*	25 6/–

LM = left median nerve; LT = left tibial nerve, L = left, RM = right median nerve; RT = right tibial nerve, R = right, – = absent cortical response, * = absent N13 wave

were an absence of response on both sides in 15 patients, an unstable response on both sides in 3 patients, and an unstable and asymmetric response on one side in 2 patients. Abnormalities in the palms were observed in 5 patients, in which bilateral palmar responses were absent. In addition, an asymmetric response was noted in 3 other patients. When there was an asymmetry of SSR responses, the SSR was disturbed on the side where motor paresis in the legs was more prominent. Four patients with a disturbed SSR in the palms also showed abnormalities in the soles, and only 1 patient (Case 1, with cerebral and brainstem lesions) had an abnormality confined to the palms with preservation of the response in the soles. Two patients (Cases 21, 22) with lesions at T4 or T5 also had absent to asymmetric response in the palms. SEPs and VEPs were abnormal in 22 and 21 out of 28 patients, respectively.

Comparing the results of SSRs and SEPs, SSRs were disturbed but SEPs were normal in 4 patients (fig. 5). On the other hand, SEPs were disturbed with preservation of SSRs in 5 patients. Among 112 limbs in 28 patients, the SSR was disturbed with preservation of the SEP in 16 limbs and the SEP was disturbed with preservation of the SSR in 16 limbs. Comparing the results of SSRs and VEPs, 6 patients had normal VEPs with abnormal SSRs and 6 had normal SSRs with abnormal VEPs.

For SSRs and/or SEPs, SSRs and/or VEPs, and SEPs and/or VEPs, abnormal results were noted in 92.8%, 96.4% and 92.8% of the subjects, respectively. When the results of 3 tests were combined, the abnormality increased to 100%.

In 2 MS patients (Cases 16, 25) with an acute exacerbation of transverse myelopathy which had almost completely recovered, we examined SSRs several times before and after the exacerbation. In Case 16, the SSR normalized before the sensory disturbance improved (fig. 6). On the other hand, in Cases 25, SSR abnormality persisted after somatic functions were almost fully restored.

TABLE 4. SITE OF LESIONS, AND RESULTS OF VEPs, SEPs AND SSRs IN PATIENTS WITH MS

		Sites of lesions							*SEPs*		*SSRs*	
Case	*Age/sex*	*Cr*	*OP*	*BS*	*Cv*	*UT*	*LT*	*VEPs*	*RM/LM*	*RT/LT*	*RP/LP*	*RS/LS*
1	55/M	+		+				A	A/A	A/A	−/−	N/N
2	18/F	+	+	+				A	A/N	A/N	N/N	N/N
3	47/F	+	+	+				A	N/A	N/A	N/N	±/±
4	52/M	+	+	+	+			A	A/A	A/A	−/−	−/−
5	50/F			+				N	A/N	A/N	N/N	N/N
6	39/F		+	+				A	N/A	N/A	N/N	N/N
7	61/F	+	+		+			A	A/A	N/A	N/N	±/±
8	28/F		+		+			A	N/N	N/N	N/N	N/N
9	56/F	+	+			+		A	N/N	N/N	N/N	−/−
10	66/F		+	+		+		A	A/N	A/N	N/N	N/N
11	38/M		+		+	+		A	A/N	A/A	↓/N	−/−
12	71/F		+		+	+		A	N/A	A/A	−/−	−/−
13	40/F	+	+		+	+		A	A/N	A/A	−/−	−/−
14	26/F				+		+	N	N/N	N/N	N/N	−/−
15	57/F	+			+	+		N	N/N	A/A	N/N	−/−
16	21/F	+	+			+		A	N/N	N/N	N/N	−/−
17	55/F	+	+			+		A	N/N	N/N	N/N	N/N
18	51/F		+			+		A	N/N	A/A	N/N	−/−
19	49/F		+			+		A	N/N	A/N	N/N	±/N
20	28/M		+			+	+	A	N/N	A/A	N/N	−/−
21	35/F					+		N	N/N	A/A	↓/N	−/−
22	54/F		+			+		A	N/N	N/A	−/−	−/−
23	22/M		+			+		A	N/N	A/A	N/N	N/N
24	43/F					+		N	N/N	A/A	N/N	±/±
25	46/M					+		N	N/N	N/N	N/N	−/−
26	51/M	+					+	N	N/A	N/A	N/N	−/−
27	26/F		+				+	A	N/N	N/A	N/N	N/±
28	67/F		+				+	A	N/A	A/A	N/↓	−/−
Incidence of abnormality								21/28	13/28	22/28	5/28	20/28
									22/28		21/28	

A = abnormal; BS = brainstem; Cr = cerebrum; Cv = cervical cord; F = female; M = male; LT = left tibial nerve; LP = left palm; LS = left sole; LT = lower thoracic cord; LM = left median nerve; OP = optic nerve; N = normal; RT = right tibial nerve; RP = right palm; RS = right sole; RM = right median nerve; UT = upper thoracic cord; − = no response; ± = unstable response; ↓ = asymmetric response.

DISCUSSION

The SSR has been adopted for the evaluation of the sympathetic system in many electromyography laboratories, but its methodology has not been fully established. In most reports, the electrical stimulation was delivered to the median nerve at the wrist. However, Uncini *et al.* (1988) indicated that an absent SSR to electrical stimulation might be due not only to dysfunction of sympathetic efferent nerve fibres, but also to abnormalities of the sensory afferent fibres. In addition, since in the spinal cat the GSR is much reduced in amplitude, but not abolished when the stimulation is delivered below the level of spinal transection (spinal GSR) (Wang and Brown, 1956*b*), stimulation below the spinal lesion is not considered to be adequate for the evaluation of myelopathy. We therefore routinely deliver the electrical stimulation to the supraorbital nerves bilaterally on the forehead, where the afferent pathway of the SSR is not disturbed by a spinal cord lesion.

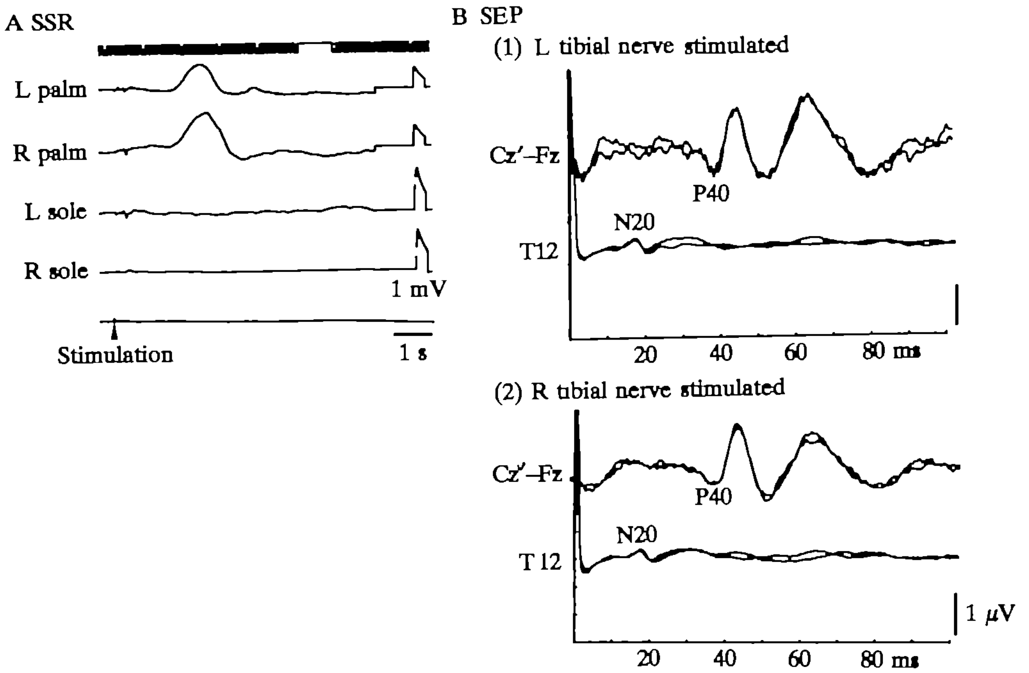

FIG. 5 SSR (A) and SEP (B) in MS *Case 17* with thoracic lesions. Although lower limb SEPs were normally recorded, plantar SSR responses were absent.

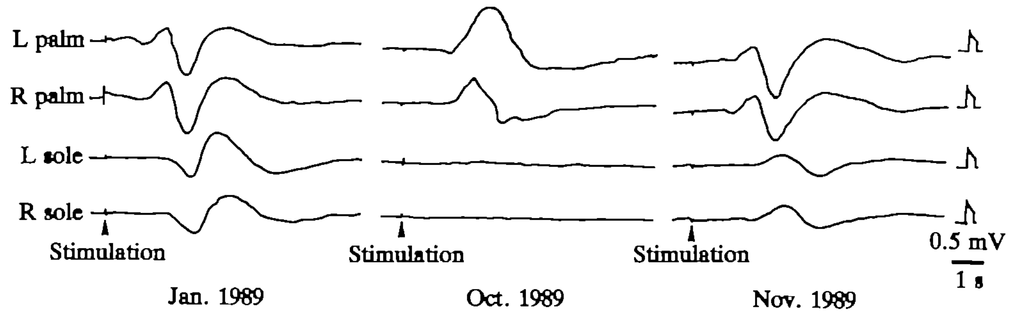

FIG. 6. SSRs in MS *Case 16*. The SSR responses from the soles disappeared bilaterally following the acute exacerbation of transverse myelopathy at the level of T8 in October 1989. These responses reappeared in November 1989 when sensory impairment was still present, although the paraparesis had almost fully recovered.

Although Knezevic and Bajada (1985) used the sequential averages of a set number of responses, we estimate the largest amplitude in more than 10 responses, as done in other studies, because the averaging method has the problems of habituation and phase cancellation.

The great variability of the SSR makes amplitude unreliable as an index of abnormality. For this reason, all previous studies have considered the SSR to be abnormal only when it is absent. However, this makes the sensitivity of the test insufficient. Judging from the results in positive and negative controls, we consider another type of response to be abnormal. This is the 'unstable response'. In patients with a functionally incomplete transection of the spinal cord caused by spinal tumour or injury, the plantar responses sometimes disappear while palmar responses are consistently recorded. Although SSRs often habituate, all responses in both the palms and soles simultaneously disappear when they habituate. Therefore, we consider it abnormal when the response in one site is sometimes absent while those in the other sites are consistently recorded. Since the ratio of left and right amplitudes varies much less than the amplitude of the response itself, the response with the smaller amplitude could be disturbed when the amplitude of the response on one side is much less than that on the contralateral side in the palms or soles. However, waveforms of SSRs vary between and even within subjects from test to test and what the amplitude of SSR reflects remains unsolved. In this study, therefore, we do not consider an asymmetric response to be abnormal though it may be an important observation.

The studies in patients with a functionally complete transection of the spinal cord revealed some important findings. In 4 patients with a lesion at T3–6, both palmar and plantar responses disappeared, and in 4 out of 5 patients with a lesion at T11 and 12, responses were also observed in the soles. These findings suggest that the central pathway mediating the SSR, which is completely different from that of the somatic nervous system, first descends to the upper thoracic cord distributing palms and then to the lower thoracic cord to reach the soles. In Case K with a Brown-Séquard syndrome due to a unilateral lesion at the T4, the amplitude of the ipsilateral palmar response was much less than that on the contralateral side. This might suggest that the descending pathway in the spinal cord mainly distributes to the ipsilateral palm.

Fuhrer (1971) studied the GSR by electrical stimulation on the neck in patients with a complete transection of spinal cord at T5–12. He found responses both in the soles and palms of patients with lesions at T10–12. The results in patients with lower thoracic lesions were similar to those in our study.

It has been stated that the source of the spinal preganglionic automatic outflow is provided by the intermediolateral nucleus which is present from T1 down to L2. The level of the spinal sympathetic outflow to the upper limbs is considered to be between T1 and T9, and that to the lower extremities between T8 and L2 (Pick, 1970). Our SSR results in patients with complete spinal transection were thus compatible with anatomical knowledge of the sympathetic system.

Of our MS patients, 75% had an abnormal SSR. Since they had no sensory disturbance in the trigeminal area, the SSR abnormality is probably attributable to disturbances of the efferent pathway in the central nervous system. Comparable with the results in positive controls for myelopathy, the SSR was abnormal both in the palms and soles in 2 MS patients who had lesions in the optic nerve and at T4 or T5. The incidence of SSR abnormality in the soles (71.4%) was much greater than that in the palms (17.9%). This is, we suspect, due to the high incidence of thoracic cord involvement in our patients: 21 of 28 patients had thoracic lesions, and 17 patients had abnormal plantar responses. In Japanese patients, both the optic nerves and spinal cord (Devic's form) are known to be more frequently involved than in Caucasians (Okinaka, 1958; Kuroiwa and Shibasaki, 1976; Kuroiwa *et al.*, 1975; Shibasaki *et al.*, 1981). It is suspected that involvement of the descending fibres in the brainstem and spinal cord by plaques of demyelination results in an impaired SSR. In addition, involvement of the intermediolateral nucleus should be considered as a source of SSR disturbance in our MS patients because, in the Devic form, the spinal lesion is often large, extending over many segments, and involving not only the white but also grey matter (Kuroiwa, 1985).

Although the descending tract for the somatosympathetic reflex in the spinal cord has not been identified precisely, the results of cordotomies in humans (Šourek, 1964; Nathan and Smith, 1987) suggested that vasomotor and sudomotor pathways in the spinal cord seem to run in the medial part of the lateral column. Kerr and Alexander (1964) obtained vasopressor response in the monkey by the stimulation of the lateral corticospinal tract and the region between this tract and grey matter. Saper *et al.* (1976) investigated direct hypothalamoautonomic connections in the rat, cat and monkey by horseradish peroxidase and found the fibres to be scattered in the equatorial region of the lateral column.

As evidence of dysfunction of the autonomic nervous system in MS patients, minor abnormalities in cardiovascular function are known to occur. Although most MS patients had no orthostatic symptoms, recent detailed studies showed abnormalities (an increased fall in blood pressure and rise in heart rate) in an orthostatic test (Sterman *et al.*, 1985; Nordenbo *et al.*, 1989). Abnormalities were also found in 4 out of 5 studies of heart rate variation during breathing (Neubauer and Gundersen, 1978; Senaratne *et al.*, 1984; Sterman *et al.*, 1985; Pentland and Ewing, 1987; Nordenbo *et al.*, 1989), and in 3 studies of rise in blood pressure during sustained handgrip (Sterman *et al.*, 1985; Pentland and Ewing, 1987; Nordenbo *et al.*, 1989).

Noronha *et al.* (1968) studied thermal sweat function using quinzarin powder in 60 MS patients. Abnormal results were noted in 25 patients (42.5%). In 4 patients there was a total, or almost total, lack of sweating; in 7 no sweating occurred over the lower half of the body, and in 14 sweating was absent over the legs. These disturbances were commoner in those with more severe and advanced MS. Another 2 studies (Vas, 1969; Cartlidge, 1972) showed similar results for a thermal sweat test and suggested that impaired sweating is a more sensitive index of autonomic function than postural hypotension or the Valsalva test in MS patients.

The incidence of SSR abnormality (75.0%) in our MS patients was higher than that of abnormalities in the thermal sweat test. However, we cannot directly compare the results of our studies and theirs, because the SSR is considered to reflect emotional sweating, and depends on different afferent and efferent pathways from thermal sweating. In addition, the subjects may be different. As stated above, Japanese MS patients have a spinal lesion more frequently than Caucasians. Shibasaki *et al.* (1981) studied the 204 British cases and 60 Japanese cases with 'probable MS' using the same diagnostic criteria and same method of analysis and concluded that Japanese patients had more frequent and severe involvement of spinal cord and brainstem than the British patients. Although the incidence of spinal cord involvement itself was as high as 76% in British patients in their study, symptoms indicating severe involvement of spinal cord such as acute transverse myelopathy was much more frequent in Japanese patients than in British patients. Therefore, SSR abnormalities may be less frequent in Caucasian patients.

For the diagnosis of MS, various evoked potentials and the blink reflex have been used to detect lesions involving different sensory systems. The highest diagnostic yield is with the SEP, while brainstem auditory evoked potentials are the least useful (Trojaborg and Petersen, 1979; Green *et al.*, 1980; Khoshbin and Hallett, 1981). In our study, the incidence of abnormalities in SSR, SEP, VEP were 75.0%, 78.6% and 71.4%, respectively. Although the SEP and SSR have different central pathways, they are similar in reflecting the function of long tracts in the brainstem and spinal cord. The incidence of SSR abnormalities is nearly as high as that for SEP abnormalities, at least in Japanese MS patients. These results indicate that the sudomotor preganglionic sympathetic system is involved as frequently as the somatic nervous system in Japanese MS patients. Besides, 4 patients had an abnormal SSR with a normal SEP, and SEPs were disturbed with the preservation of SSRs in 5 patients. Therefore, the combination of SEP and SSR yields a higher sensitivity for the evaluation of myelopathy than the two individual yields.

In general, the usefulness of the evoked potentials is best demonstrated in asymptomatic patients. Since we did not quantitate emotional sweating, it was not clear whether the SSR can detect a subclinical lesion or not. However, most patients do not notice the disturbance of sweating and it is not easy to evaluate dysfunction definitely for emotional sweating. Another test for sudomotor sympathetic function, that is, the thermal sweat test, causes patient discomfort and is time-consuming, while SSR is simple and easy both for patient and examiner (it only takes 15 min). The SSR is therefore a valuable test for providing objective information on the sympathetic system which is difficult to evaluate precisely by physical examination. Since the sensitivity of the SSR was as high as that for other evoked potentials in MS patients, it is expected to provide a new method for the detection of lesions. However, further investigation on the supraspinal mechanism of the SSR is necessary for precise interpretation.

REFERENCES

CARTLIDGE NEF (1972) Autonomic function in multiple sclerosis. *Brain*, **95**, 661–664.

FÉRÉ C (1888) Note sur les modifications de la resistance électrique sous l'influence des excitations sensorielles et des emotions. *Compte Rendus des Séances de la Société de Biologie et de ses Filiales, Paris*, **5**, 217–219.

FUHRER MJ (9171) Analysis of electrodermal evidence for a paramedullary afferent tract in patients with a transection of the thoracic spinal cord. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 281–288.

GREEN JB, PRICE R, WOODBURY SG (1980) Short-latency somatosensory evoked potentials in multiple sclerosis: comparison with auditory and visual evoked potentials. *Archives of Neurology, Chicago*, **37**, 630–633.

HAGBARTH K-E, HALLIN RG, HONGELL A TOREBJORK HE, WALLIN BG (1972) General characteristics of sympathetic activity in human skin nerves. *Acta Physiologica Scandinavica*, **84**, 164–176.

KERR FWL, ALEXANDER S (1964) Descending autonomic pathways in the spinal cord. *Archives of Neurology, Chicago*, **10**, 249–261.

KHOSHBIN S, HALLETT M (1981) Multimodality evoked potentials and blink reflex in multiple sclerosis. *Neurology, New York*, **31**, 138–144.

KNEZEVIC W, BAJADA S (1985) Peripheral autonomic surface potential: a quantitative technique for recording sympathetic conduction in man. *Journal of the Neurological Sciences*, **67**, 239–251.

KUROIWA Y (1985) Neuromyelitis optica (Devic's disease, Devic's syndrome). In: *Handbook of Clinical Neurology*, Volume 47. Edited by P. J. Vinken, G. W. Bruyn and H. L. Klawans. Amsterdam. Elsevier, pp. 397–408.

KUROIWA Y, IGATA A, ITAHARA K, KOSHIJIMA S, TSUBAKI T, TOYOKURA Y *et al.* (1975) Nationwide survey of multiple sclerosis in Japan: clinical analysis of 1,084 cases. *Neurology, Minneapolis*, **25**, 845–851.

KUROIWA Y, SHIBASAKI H (1976) Epidemiologic and clinical studies of multiple sclerosis in Japan. *Neurology, Minneapolis*, **26**, Supplement, 8–10

LANGWORTHY OR, RICHTER CP (1930) The influence of efferent cerebral pathways upon the sympathetic nervous system. *Brain*, **53**, 178–193.

MASELLI RA, JASPAN JB, SOLIVEN BC, GREEN AJ, SPIRE J-P, ARNASON BGW (1989) Comparison of sympathetic skin response with quantitative sudomotor axon reflex test in diabetic neuropathy. *Muscle and Nerve*, **12**, 420–423.

NATHAN PW, SMITH MC (1987) The location of descending fibres to sympathetic preganglionic vasomotor and sudomotor neurons in man. *Journal of Neurology, Neurosurgery and Psychiatry*, **50**, 1253–1262.

NEUBAUER B, GUNDERSEN HJG (1978) Analysis of heart rate variations in patients with multiple sclerosis: a simple measure of autonomic nervous disturbances using an ordinary ECG. *Journal of Neurology, Neurosurgery and Psychiatry*, **41**, 417–419.

NIAKAN E, HARATI Y (1988) Sympathetic skin response in diabetic peripheral neuropathy. *Muscle and Nerve*, **11**, 261–264.

NORDENBO AM, BOESEN F, ANDERSEN EB (1989) Cardiovascular autonomic function in multiple sclerosis. *Journal of the Autonomic Nervous System*, **26**, 77–84.

NORONHA MJ, VAS CJ, AZIZ H (1968) Autonomic dysfunction (sweating responses) in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **31**, 19–22.

OKINAKA S, TSUBAKI T, KUROIWA Y, TOYOKURA Y, IMAMURA Y, YOSHIKAWA M (1958) Multiple sclerosis and allied diseases in Japan: clinical characteristics. *Neurology, Minneapolis*, **8**, 756–763.

PICK J (1970) Central autonomic connections. In: *The Autonomic Nervous Sytem: Morphological, Comparative, Clinical and Surgical Aspects*. Edited by J. Pick. Philadelphia: J. B. Lippincott, pp. 61–102

PENTLAND B, EWING DJ (1987) Cardiovascular reflexes in multiple sclerosis. *European Neurology*, **26**, 46–50.

POSER CM, PATY DW, SCHEINBERG L, MCDONALD WI, DAVIS FA, EBERS GC *et al.* (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, **13**, 227–231.

SAPER CB, LOEWY AD, SWANSON LW, COWAN WM (1976) Direct hypothalamo-autonomic connections. *Brain Research, Amsterdam*, **117**, 305–312.

SENARATNE MPJ, CARROLL D, WARREN KG, KAPPAGODA T (1984) Evidence for cardiovascular autonomic nerve dysfunction in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 947–952.

SHAHANI BT, HALPERIN JJ, BOULU P, COHEN J (1984) Sympathetic skin response—a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 536–542.

SHIBASAKI H, MCDONALD WI, KUROIWA Y (1981) Racial modification of clinical picture of multiple sclerosis: comparison between British and Japanese patients. *Journal of the Neurological Sciences*, **49**, 253–271.

SOLIVEN B, MASELLI R, JASPAN J, GREEN A, GRAZIANO H, PETERSEN M *et al.* (1987) Sympathetic skin response in diabetic neuropathy. *Muscle and Nerve*, **10**, 711–716.

ŠOUREK K (1964) Die Bedeutung des galvanischen Hautreflexes für die Lokalisation von Läsionen im Nervensystem des Menschen. *Acta Neurochirurgica*, **11**, 518–529.

STERMAN AB, COYLE PK, PANASCI DJ, GRIMSON R (1985) Disseminated abnormalities of cardiovascular autonomic functions in multiple sclerosis. *Neurology, Cleveland*, **35**, 1665–1668.

TROJABORG W, PETERSEN E (1979) Visual and somatosensory evoked cortical potentials in multiple sclerosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **42**, 323–330.

UNCINI A, PULLMAN SL, LOVELACE RE, GAMBI D (1988) The sympathetic skin response: normal values, elucidation of afferent components and application limits. *Journal of the Neurological Sciences*, **87**, 299–306.

VAS CJ (1969) Sexual impotence and some autonomic disturbances in men with multiple sclerosis. *Acta Neurologica Scandinavica*, **45**, 166–182.

WANG GH (1957) The galvanic skin reflex: a review of old and recent works from a physiologic point of view. Part 1. *American Journal of Physical Medicine*, **36**, 295–320.

WANG G-H, RICHTER CP (1928) Action current from the pad of the cat's foot produced by stimulation of the tuber cinereum. *Chinese Journal of Physiology*, **2**, 279–284.

WANG GH, LU TW (1930) Galvanic skin reflex induced in the cat by stimulation of the motor area of the cerebral cortex. *Chinese Journal of Physiology*, **4**, 303–326.

WANG GH, STEIN P, BROWN VW (1956*a*) Brainstem reticular system and galvanic skin reflex in acute decerebrate cats. *Journal of Neurophysiology*, **19**, 350–355.

WANG GH, BROWN VW (1956*b*) Changes in galvanic skin reflex after acute spinal transection in normal and decerebrate cats. *Journal of Neurophysiology*, **19**, 446–451.

WATAHIKI Y (1987) Sympathetic skin response (SSR): a simple quantitative method for assessing sympathetic dysfunction. (2) SSR in diabetic neuropathy. *Autonomic Nervous System, Tokyo*, **24**, 557–565.

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ALTERED CORTICOSPINAL PROJECTIONS TO LOWER LIMB MOTONEURONS IN SUBJECTS WITH CEREBRAL PALSY

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SUMMARY

The projections of cortical neurons activated by transcranial magnetic stimulation to the motoneurons of lower limb muscles were examined in 22 normal subjects and 14 subjects with cerebral palsy (CP). In normal subjects, magnetic stimulation produced strong facilitation of tibialis anterior (TA) motoneurons, but little or no facilitation of soleus (SOL) motoneurons. This differential facilitation of TA and SOL motoneurons was observed at all stimulus sites on the scalp and all stimulus intensities at which responses could be elicited. In subjects with CP, magnetic stimulation produced almost equal facilitation of TA and SOL motoneurons. This could not be explained by differences in the excitability of the respective motoneuron pools. It is postulated that the projections from the motor cortex to spinal motoneurons are altered in CP. These abnormal projections may contribute to the impairment of voluntary movements experienced by these subjects

INTRODUCTION

Cerebral palsy (CP) is a general term used to describe nonprogressive disorders of movement and posture due to defects or damage to the developing brain (Bax, 1964). The motor disorders are classified according to the pattern of paresis and the presence of involuntary or poorly coordinated movements (Ingram, 1964). The most common disorder is spastic diplegia (Barabas and Taft, 1986).

The neurophysiological abnormalities which underlie the various motor disorders of CP are unknown. One abnormality which has frequently been observed is a failure of the normal reciprocal relationship between agonist and antagonist muscles during voluntary movements. Milner-Brown and Penn (1979) recorded electromyograms (EMGs) of upper and lower limb muscles during voluntary flexion and extension movement in 20 patients with CP (spastic quadriplegia or athetosis). They found the antagonist to be active throughout the movement in many patients and, in 6 patients, there was a complete breakdown of the reciprocal relationship resulting in cocontractions of flexor/extensor muscle pairs. Hallett and Alvarez (1983) studied rapid voluntary elbow flexion movements in 14 patients with athetoid CP and found that the majority of patients showed disruption of the normal triphasic pattern of muscle activation in biceps and triceps, often with inappropriate activation of the antagonist triceps. Dietz and Berger (1983) examined the EMG patterns of the ankle flexors and extensors during locomotion in patients with CP (spastic diplegia) and in patients with adult onset spasticity. They

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found that coactivation was prominent during the stance phase in patients with CP, but not in patients with adult onset spasticity. The cocontractions observed during voluntary movements could be due to abnormalities at the segmental level. This hypothesis received support from Gottlieb *et al.* (1982) and Myklebust *et al.* (1982) who observed simultaneous activation of tibialis anterior and soleus muscles following Achilles tendon taps and passive dorsiflexion of the ankle. They advanced the attractive hypothesis that segmental reciprocal inhibition might be replaced by reciprocal facilitation in patients with CP. Berbrayer and Ashby (1990), however, found reciprocal inhibition to be normal in 15 patients with CP.

An alternative explanation for the cocontraction of muscles during voluntary movements in CP is that the projections of descending pathways to motoneurons are abnormal (Milner-Brown and Penn, 1979). To explore this possibility, the projections from the motor cortex to lower limb spinal motoneurons in normal subjects and subjects with CP were compared in the present study. A preliminary report has been published (Brouwer and Ashby, 1990*a*).

METHODS

Studies were carred out on normal subjects and subjects with CP with informed consent. Subjects were screened to ensure they had no intracranial metal implants, no cardiac pacemakers and no history of epilepsy. Magnetic resonance images (MRI) of the brain were obtained from some of the subjects with CP to exclude anatomical abnormalities. A clinical neurological examination was performed on all subjects with CP to document the degree of motor impairment. The protocol was approved by the local ethical review board.

Stimulation

A Cadwell MES-10 electromagnetic stimulator was used to excite neurons in the brain. When this device is triggered, capacitors discharge and cause a current to flow through a 14 turn circular coil (inside and outside diameter of 7.5 cm and 9.0 cm, respectively). This current results in a varying magnetic field which, in turn, induces circular currents in nearby conducting tissues. These currents are proportional to the rate of change of the magnetic field and the initial stored charge (Barker *et al.*, 1987) which is set according to a linear scale ranging from 0% to 100%. The maximum magnetic field strength of this stimulator is 2 tesla (according to the manufacturer's specifications) and the induced current waveform is a damped sinusoid with an initial peak at approximately 5 μs and a reversed peak at approximately 135 μs.

Experimental procedures

Recordings with surface electrodes. Subjects lay comfortably on a bed (supine) and were instructed to relax. Surface EMG electrodes (gold-plated discs, 7 mm in diameter) were placed 3 cm apart over the bellies of 8 upper and lower limb muscles bilaterally, including tibialis anterior (TA) and soleus (SOL). EMG responses were bandpass filtered at 10 Hz–2 kHz, amplified to 0.5 mV/div and recorded for a 200 ms period which included a 20 ms prestimulus segment. If any EMG activity was present during the prestimulus portion, the recording was discarded and repeated with the subject relaxed. Responses were digitized and the data stored on a laboratory computer for later analysis.

Compound muscle action potentials (CMAPs) were recorded in response to single magnetic stimuli delivered with the coil positioned over the motor cortex with its centre aligned midway between Cz and C3 (Cz-C3) and then midway between Cz and C4 (Cz-C4) according to the International 10-20 System (Jasper, 1958). When stimulating over the left hemisphere the current flowed clockwise through the coil as viewed from above and, when stimulating over the right hemisphere, counterclockwise. The stimulus intensity was increased in 5% increments of the stimulator's maximum output until a response was evoked in either TA or SOL. This intensity was termed 'threshold' (T). The stimulus was then further increased to T+5% and T+10%. Three EMG recordings were made at each intensity at both stimulus sites. The 3 EMG records from each muscle (for a given stimulus site and intensity) were averaged and the peak-to-peak CMAP amplitudes measured from the averaged EMG trace. The amplitudes were expressed as a percentage of the maximum M wave of that muscle produced by supramaximal electrical stimulation of the respective muscle's nerve. This is referred to as the 'relative amplitude' (% max M).

Single motor unit recordings

Single motor unit recordings were obtained from the TA and SOL muscles and, in some studies, from the medial gastrocnemius (MG) muscle. A concentric needle electrode with a recording surface area of 0.07 mm^2 (Dantec 13L49) was positioned near a motor unit activated by gentle voluntary contraction. Single motor unit action potentials identifiable by their characteristic shape (bandpass filtered at 10 Hz – 10 kHz) were extracted with a window discriminator and displayed on a storage oscilloscope using a delay line. The pulse from the discriminator led to a loudspeaker and tachometer. Subjects were provided with visual and auditory feedback of the unit's discharges and its instantaneous firing rate. Subjects kept the unit discharging steadily while a minimum of 100 magnetic stimuli were delivered at 3 s intervals with the coil positioned over the contralateral cortex (Cz-C3 or Cz-C4) The intensity of stimulation was well below that which resulted in a muscle contraction in the voluntarily contracted TA (or SOL) muscle.

Peristimulus time histograms (PSTHs) with 1 ms bins were used to record changes in the firing probability of the selected motor unit produced by the magnetic stimulus. The mean background firing probability was calculated from the 100 ms prestimulus portion of each PSTH. A period of increased firing probability was defined as a coherent cluster of at least 3 bins with amplitudes greater than the mean background plus 2 SDs (*see* Mao *et al.*, 1984, for details of the method). The area of the peak of increased firing probability above the mean background level (expressed as extra counts per 1000 stimuli) provided an estimate of the amplitude of the underlying composite excitatory postsynaptic potential (EPSP) produced by the descending cortical volley. The duration of the PSTH peak reflected the EPSP rise time (Ashby and Zilm, 1982; Fetz and Gustaffson, 1983; Cope *et al.*, 1987; Midroni and Ashby, 1989).

RESULTS

Recordings were obtained from 22 neurologically normal subjects (mean age ± 1 SD = 28 ± 10 yrs) and 14 subjects with CP (mean age ± 1 SD = 22 ± 7 yrs). There were 9 subjects with spastic diplegia, 3 with athetosis, 1 with ataxia and 1 with left hemiplegia. A summary of the clinical findings for each subject is presented in Table 1.

TABLE 1 SUMMARY OF THE CLINICAL FINDINGS IN SUBJECTS WITH CP

				Tone		*Strength*		*Tendon reflexes*	
Subject	*Classification*	*Age (yrs)*	*Aetiology*	*UE*	*LE*	*UE*	*LE*	*UE*	*LE*
SG	Diplegic	25	Premature	N	+	N	+	N	+
HA	Diplegic	20	Premature	N	+	N	−	N	+
GV	Diplegic	31	Unknown	N	+	N	+	N	+
JB	Diplegic	32	Premature	N	+	N	−	N	+
AF	Diplegic	16	Premature	N	+	N	−	+	+
DaL	Diplegic	14	Premature	N	+	N	−	N	+
JM*	Diplegic	34	Premature	N	+	N	−	N	N
DW*	Diplegic	25	Premature	N	+	N	−	N	+
SC*	Diplegic	25	Unknown	N	+	N	−	N	+
NN	Athetoid	18	Anoxia	+	+	−	−	+	+
GG	Athetoid	17	Unknown	+	+	−	−	+	+
DeL	Athetoid	14	Premature	+	+	−	−	+	+
PC	Ataxic	19	Anoxia	N	−	N	N	N	N
GR	L. hemiplegic	24	Anoxia	+	+	−	−	N	+

* Single unit study only, N = normal, + = increased; − = decreased, UE = upper extremity, LE = lower extremity.

Recordings with surface electrodes

Surface EMG recordings were obtained from 11 normal subjects and 11 subjects with CP (7 with spastic diplegia, 2 with athetosis, 1 with ataxia and 1 with hemiplegia). In all normal subjects and 9/11 subjects with CP, magnetic stimulation applied over Cz-C3 and Cz-C4 resulted in short-latency CMAPs in the relaxed contralateral muscles of the upper and lower limbs. No short-latency responses were observed in the 2 subjects with athetosis. In this paper only responses elicited in TA and SOL are considered. One normal subject and 1 subject with CP did not demonstrate lower limb responses although short-latency activation of upper limb muscles was apparent.

Examples of typical surface recordings are shown in fig. 1. In the normal subject (top) there was strong activation of TA, but SOL remained silent. In a subject with CP (bottom) TA and SOL were activated equally. These were consistent findings. Fig. 2 shows the mean of the relative amplitudes of the contralateral lower limb responses at stimulus intensities at and above threshold. Since there were no differences between the amplitudes of the contralateral responses elicited by stimulation over the left or right hemisphere at any given intensity ($P > 0.70$) these data were pooled (only the results from the affected side of the hemiplegic subject were included). In normal subjects, but not subjects with CP, the mean of the relative amplitudes of the TA responses were significantly larger than those of SOL ($P < 0.01$) at all stimulus intensities. In the subjects with CP, the means of the relative amplitudes of the SOL responses were significantly greater than those of normal subjects ($P < 0.05$ at T; $P < 0.01$ at T+5%; $P < 0.005$ at T+10%). It was considered unlikely that the responses recorded over SOL were due to volume conduction from TA since the action potenials had different configurations and in some cases the responses were larger from SOL than from TA (*see* fig. 1, bottom).

To determine whether the observed pattern of TA and SOL activation was related to a particular site of stimulation, magnetic stimuli were applied at various scalp locations

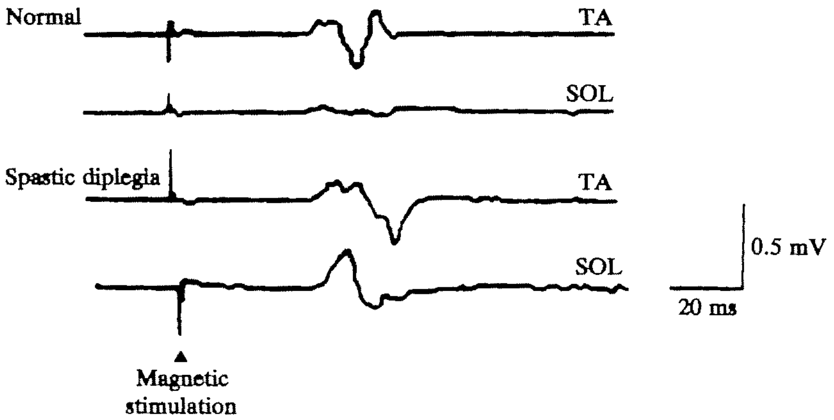

FIG 1. Compound muscle action potentials (CMAPs) from the relaxed tibialis anterior (TA) and soleus (SOL) muscles of 2 subjects following magnetic stimulation applied to the contralateral hemisphere at an intensity of 10% above 'threshold'. Each trace represents the average of 3 recordings. Note that in a normal subject (*top*) there was short-latency activation of TA, but little or no activation of SOL. In a subject with spastic diplegia (*bottom*) there was short-latency activation of both TA and SOL muscles.

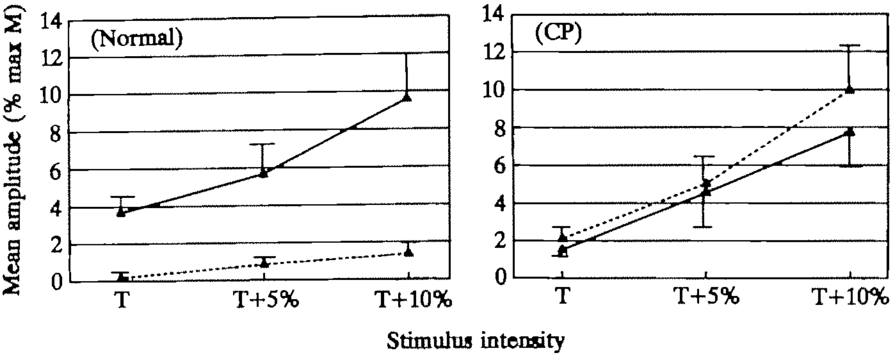

FIG. 2. Means of the relative amplitudes (+1 SE) of the contralateral responses recorded from TA (filled triangles) and SOL (open triangles) following magnetic stimulation (pooled data from Cz-C3 and Cz-C4 stimulation sites) from 10 normal subjects (*left*) and from 8 subjects with CP (*right*). Normal subjects showed significantly greater activation of TA than SOL ($P < 0.01$ at all intensities), whereas in the subjects with CP, the activation of the 2 muscles was similar. The amplitudes of the CMAPs are expressed as a percentage of that muscle's maximum M wave (% max M).

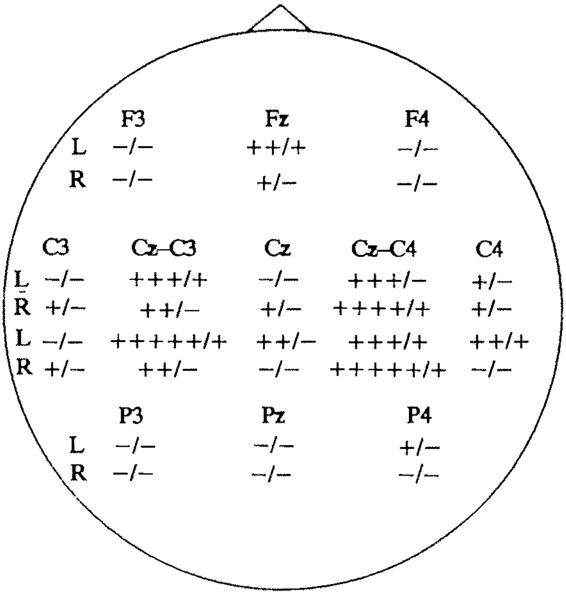
F3
Fz
F4
L −/− ++/+ −/−
R −/− +/− −/−
C3
Cz-C3
Cz
Cz-C4
C4
L −/− +++/+ −/− +++/− +/−
R +/− ++/− +/− ++++/+ +/−
L −/− +++++/+ ++/− +++/+ ++/+
R +/− ++/− −/− +++++/+ −/−
P3
Pz
P4
L −/− −/− +/−
R −/− −/− −/−

FIG. 3. A comparison of the relative amplitudes of the TA and SOL (TA/SOL) responses evoked by magnetic stimulation applied over several scalp locations at an intensity of 'threshold' + 10% in a normal subject An absence of a response is indicated by '−'. The relative amplitudes of responses are indicated in multiples of 2% max M by '+'. The responses evoked in the left (L) and right (R) limbs are shown when stimulating with the current flowing through the coil in a clockwise direction. For those sites along the midcoronal line, stimuli were also applied with the current flowing through the coil in a counter-clockwise direction (second group of TA/SOL comparisons). Note that the response in TA is always greater than that in SOL.

in 1 normal right handed subject. The stimulating coil was placed flat on the scalp with its centre positioned successively over F3; Fz, F4, C3, Cz-C3, Cz, Cz-C4, C4, P3, Pz and P4. A stimulus intensity of T+10% ('threshold' was determined at the Cz-C3 site) was selected in order to reduce the likelihood of missing responses due to insufficient stimulus strength. The relative response amplitudes of TA were greater than SOL at all sites from which responses could be obtained (fig. 3).

Single unit recordings

Recordings from single motor units in TA and SOL were obtained from 13 normal subjects and 6 subjects with spastic diplegia. Magnetic stimulation was applied over the contralateral hemisphere at an intensity which was subthreshold for activating the relaxed TA or SOL muscles. Examples of typical recordings are shown in fig. 4. In normal subjects 13/13 of the TA units studied showed a short-latency (24 − 31 ms), brief facilitation whereas only 3/13 (23%) SOL motor units showed short-latency facilitation (28 − 32 ms) in response to the same intensity stimulus. The mean number of displaced counts (normalized to 1000 stimuli) in the short-latency PSTH peak was 259 for TA and 20 for SOL ($P < 0.001$; fig. 5, left). The results are summarized in Table 2. In

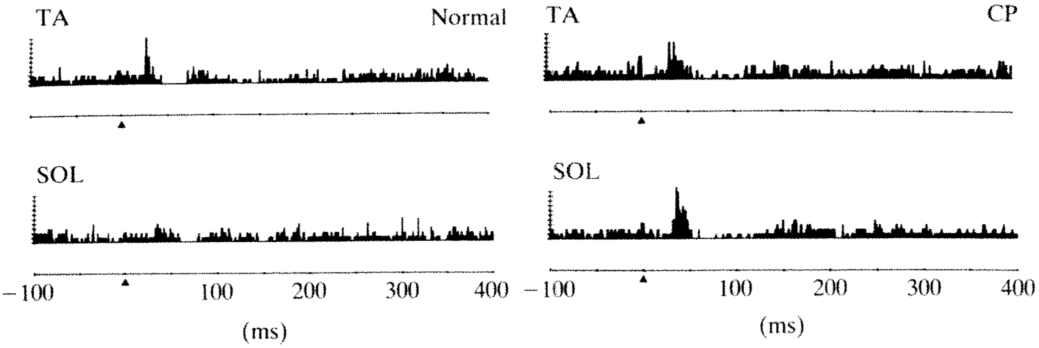

FIG. 4. Representative PSTHs from 2 subjects showing changes in the firing probability of single TA and SOL motoneurons in response to 100 magnetic stimuli subthreshold for a muscle contraction applied at time zero (arrow). In the normal subject (*left*) there is a brief, short-latency period of increased firing probability in the TA motor unit, but not in the SOL motor unit. In the subject with CP (*right*) both the TA and SOL motor units show similar short-latency facilitation. Stimulus intensity settings were 65% for the normal subject and 60% for the subject with CP.

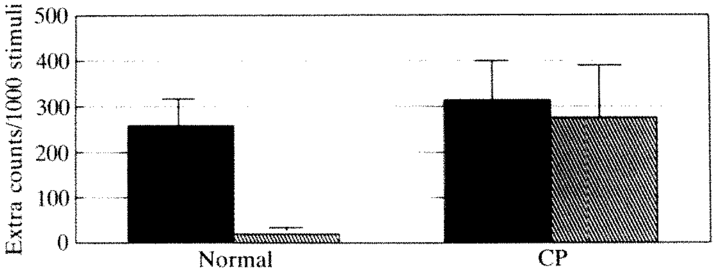

FIG. 5. The mean amplitudes (+1 SE) of the periods of increased firing probability (expressed as extra counts per 1000 stimuli) in TA (filled areas) and SOL (hatched areas) motor units from 13 normal subjects and 6 subjects with CP. In normal subjects the facilitation was much greater for TA than for SOL motoneurons ($P < 0.001$), but in subjects with CP there was equal facilitation of both types of motoneuron. The facilitation of SOL motoneurons was significantly greater than that for normal subjects ($P < 0.005$).

1 subject with CP, no responses were observed in either muscle, perhaps due to insufficient stimulus strength. The remaining subjects all showed almost equal short-latency facilitation of TA and SOL motor units. An example is shown in fig. 4. The strength of the SOL facilitation was significantly greater in subjects with CP than normal subjects ($P < 0.005$, fig. 5). There was no difference in the average stimulus intensity used for the normal subjects (57.4%) or subjects with CP (60.2%), $P > 0.95$.

TABLE 2 CHARACTERISTICS OF THE SHORT-LATENCY FACILITATIONS IN TA AND SOL MOTONEURONS

	Muscle	*Response frequency (%)*	*Mean onset latency (ms)**	*Mean duration (ms)**	*Extra counts/ 1000 stimuli**
Normal	TA	100	26.5±0.6	5.3±0.6	259±50
(n = 13)	SOL	23	30.0±1.0	3.3±0.9	20±10
CP	TA	83	28.8±0.6	8.4±1.4	314±77
(n = 6)	SOL	83	31.0±1.2	9.0±2.3	276±108

* Means ± 1 SEM

The lack of activation of SOL motor units in normal subjects could not be attributed to inadequate stimulation. Increasing the stimulus intensity to 5% above that at which a large facilitation of TA motor units was recorded did not alter the profiles of the PSTHs generated from the SOL motor units in the 5 subjects in whom this was tried. This point is also supported by the surface EMG recordings (fig. 2). The amplitude of the SOL CMAPs, unlike those of TA, do not increase with increasing stimulus intensity.

The characteristics of the short-latency facilitations of TA and SOL motor units for both groups are summarized in Table 2. The mean duration of the PSTH peaks from TA was longer in subjects with CP than in normal subjects ($P < 0.05$). There is, however, a positive relationship between the magnitude of a PSTH peak and its duration (Mailis and Ashby, 1990) which may account for this. When peak area is plotted against peak duration for normal subjects and for subjects with CP (fig. 6, circles) the slopes

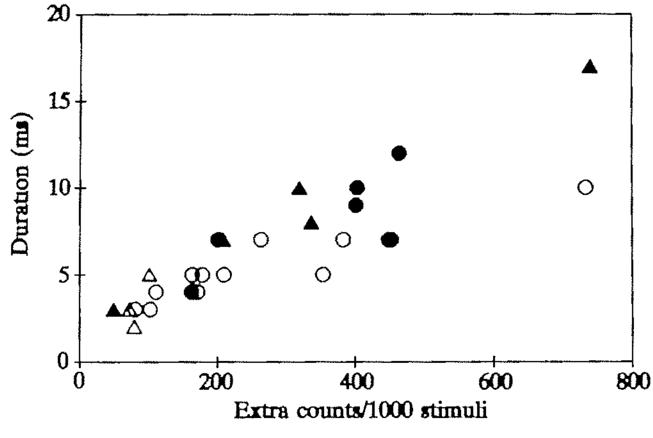

FIG 6. The relationship between the magnitude and duration of the PSTH peaks obtained from TA motor units (normal subjects, open circles; subjects with CP, filled circles) and from SOL motor units (normal subjects, open triangles; subjects with CP, filled triangles).

of the regression lines for the two groups were similar ($P > 0.05$). Thus the slightly longer mean duration of the PSTH peaks in subjects with CP can be explained by their larger size. The wider peaks of SOL facilitation in subjects with CP may have a similar explanation (fig. 6, triangles), although the numbers were too few for statistical evaluation.

To determine whether the stronger facilitation of SOL motoneurons in CP was an isolated phenomenon or part of a more generalized process, the responsiveness of MG motoneurons to magnetic stimulation was examined in 5 normal subjects and 1 subject with CP. Short-latency MG facilitations were seen in 2/5 normal subjects and in both cases were very small in amplitude (mean number of displaced counts/1000 stimuli = 13). In contrast, the subject with CP showed a much stronger short latency facilitation of MG (182 displaced counts/1000 stimuli).

MRI findings

Magnetic resonance images of the brain were obtained for 5 subjects with CP (4 diplegic, 1 athetoid). These did not show any gross anatomical defects (hydrocephalus, atrophy, distortions of grey or white matter) which might alter the path of the currents induced in the cranium.

DISCUSSION

Threshold magnetic stimulation applied flat over the motor cortex causes short-latency facilitation of contralateral motoneurons. This activation probably results from transynaptic excitation of the fast corticospinal neurons which make monosynaptic connections to spinal motoneurons (Amassian *et al.*, 1988; Day *et al.*, 1989; Zarola *et al.*, 1989), although recently this view has been challenged with evidence of direct corticospinal activation (Edgley *et al.*, 1989, 1990). There is a distinct pattern of corticospinal projections to various motoneuron pools (Brouwer and Ashby, 1990*b*), the much greater activation of TA than SOL being a good example of this.

The selective facilitation of TA motoneurons in normal subjects cannot be attributed to the preferential excitation of certain cortical neurons as a consequence of a particular stimulus site. At any of the sites on the head from which excitation of either of these muscles could be effected, the excitation of TA was always greater than SOL. Furthermore, the cortical areas projecting to TA and SOL are likely in close proximity if not overlapping (Asanuma *et al.*, 1979). Large circular stimulating coils probably generate currents in a large volume of the underlying brain so the stimulus site is not critical. Hess *et al.* (1987) found that the stimulating coil could be moved 2 cm sagittally or coronally from the vertex without altering the amplitude or latency of the responses elicited in small hand muscles, and that the same motor unit could be activated from scalp sites up to 6 cm apart.

Anodal stimulation of the exposed cortex in nonhuman primates excites cortical cells directly (Gorman, 1966; Amassian *et al.*, 1987) and anodal stimulation applied over the human scalp is also believed to excite cortical neurons directly (Hess *et al.*, 1987; Amassian *et al.*, 1988; Day *et al.*, 1989). The pattern of muscle activation resulting from anodal and magnetic stimulation, however, is similar. Cowan *et al.* (1986), for example, using the H reflex to examine subthreshold facilitation and inhibition of motoneurons, found that anodal scalp stimulation produced descending corticospinal volleys which facilitated the H reflex of TA, but generally inhibited the H reflex of SOL (even during weak voluntary contraction of this muscle). Thus the differential effects on TA and SOL motoneurons elicited by magnetic stimulation appear to reflect the pattern of corticospinal projections to the motoneurons of these muscles and not simply the pattern of presynaptic inputs to the cortical neurons.

Responses evoked from TA and SOL in subjects with CP

In subjects with CP, magnetic stimulation evoked CMAPs in SOL which were as large as those in TA. Although most of these subjects had some wasting of the lower limb muscles, this finding could not be attributed to volume conduction of the responses in the anterior compartment to the posterior compartment. The responses recorded over SOL were often larger than those recorded over TA (*see* fig. 1). Nor can the larger CMAPs in SOL be attributed to greater background excitability of SOL motoneurons. PSTHs of single motor units in this muscle demonstrate that the differential activation of SOL motoneurons in normal subjects and subjects with CP reflect the magnitude of the short-latency EPSPs induced in these muscles by magnetic stimuli. We have no evidence that the differences in the pattern of muscle activation between normal subjects and subjects with CP are due to the differential spread of current within the cranium. The MRI scans revealed no hydrocephalus, atrophy or other gross structural abnormalities which could alter the path of the induced currents.

The large amplitude of the PSTH peaks obtained from SOL motor units in subjects with CP may be an example of a more general loss of specificity in the projections of the short-latency corticospinal pathways. In normal subjects, both SOL and MG motoneurons receive little or no facilitation from the cortex. In subjects with CP, SOL, MG and TA motoneurons all are facilitated about equally. This pattern appears to be unique to subjects with CP in whom lesions have occurred during the developmental period of the central nervous system. Cerebral infarctions causing hemiparesis in adults abolish the short-latency facilitations altogether (Yang *et al.*, 1990). Incomplete spinal cord lesions do not alter the pattern of activation of TA and SOL, although the latency of the TA facilitation is delayed (Bugaresti *et al.*, 1990).

Explanations for the altered responses in CP

One possible explanation for the findings in CP is that there are changes in segmental reflex pathways. In normal subjects, the initial response in SOL evoked by anodal stimulation of the cortex (tested using the H reflex) is inhibition (Cowan *et al.*, 1986). In the monkey this inhibition is mediated via the Ia inhibitory interneuron (Jankowska *et al.*, 1976). The loss of this inhibition might reveal facilitation of SOL motoneurons in CP. Myklebust *et al.* (1982), however, examined the pathways from TA to SOL by stretching the anterior tibial muscles and recording the surface EMG from SOL. They did not observe (in either normal or CP subjects) a facilitation of SOL by TA stretch. Alternatively there may be aberrant segmental projections from the cortex to the SOL motoneurons in CP. Studies in animals (reviewed below) indicate that lesions of the immature brain can cause corticospinal pathways to develop abnormal patterns of projection (Villablanca *et al.*, 1986).

Could the altered pattern be due to changes in cortical excitability? It is unlikely that the size of the descending volley is larger in subjects with CP simply because they required more voluntary effort to contract SOL, as Brouwer *et al.* (1989) have shown that the EPSPs produced in spinal motoneurons by magnetic stimulation of the cortex are not enhanced by voluntary effort.

Finally, if magnetic stimulation activates corticospinal neurons transynaptically, the presynaptic projections to cortical neurons may be altered in CP. This could only be excluded by anodal stimulation.

Effects of early brain lesions in experimental animals

In most mammalian species the pathways extending from the cortex to the spinal cord are not fully developed at the time of birth. In the cat, for example, corticospinal neurons are present within the first 6 wks of gestation (Wise *et al.*, 1977). Their projections reach the cervical region of the spinal cord prenatally (Wise *et al.*, 1977) and the lumbar region 1 wk postnatally (Bregman and Goldberger, 1983). Despite the apparent anatomical connectivity between the motor cortex and the spinal cord, it is only after 37 to 45 postnatal days that intracortical microstimulation of the motor cortex can bring spinal motoneurons to threshold, suggesting that functional synapses have been established at this time (Bruce and Tatton, 1981). A high frequency train of electrical stimuli to the motor cortex has, however, been shown to activate contralateral forelimb muscles by the second postnatal week, although the latency is approximately 14-fold of that observed in adult cats (Amassian and Ross, 1978).

Lesions of the brain during the period of early postnatal development may cause the corticospinal pathway to develop abnormally. For example, following unilateral hemispherectomy in neonatal kittens, abnormal projections develop from the intact cortex to the opposite red nucleus (Villablanca *et al.*, 1982) and thalamus (Villablanca *et al.*, 1986) as well as to the ipsilateral dorsal column nuclei and spinal grey matter (Gómez-Pinilla *et al.*, 1986). Unilateral lesions of the corticospinal pathways in the caudal medulla in kittens result in retrograde degeneration of axotomized cells, but the cells whose axons have not yet reached the level of the lesion develop abnormal projections to the contralateral side which later decussate to terminate in the ipsilateral spinal cord (Tolbert and Der, 1987). These anatomical changes do not occur following lesions in adult animals (Villablanca *et al.*, 1986). The motor behaviours attributed to the growth of these aberrant pathways disappear, as might be expected, when the intact motor cortex or intact corticospinal tracts are lesioned (Villablanca *et al.*, 1986).

Theriault and Tatton (1989) have shown that the terminal fields of motor cortical neurons in the spinal grey matter of neonatal kittens are widely distributed bilaterally, but by 38 to 44 days postnatally have reorganized to terminate mainly in laminae IV – VII of the contralateral side (the normal adult pattern). What leads to this reorganization is unknown. Humphrey and O'Donoghue (1989) suggested that axonal elimination can account for the emergence of the adult pattern of corticospinal neuronal distribution rather than regional differences in cortical cell death. These changes they observed were associated with a reduction in the number of axons in the cord (Cox *et al.*, 1989). Theriault and Tatton (1989) speculate that early brain lesions may prevent this excess collateral elimination from occurring.

In humans, the corticospinal pathways reach the cervical cord by 17 wks and the lumbosacral cord by 29 wks of gestation (Humphrey, 1960). It is likely that the characteristic adult pattern of synaptic projections to motoneurons are not present at birth, but develop during the first postnatal year in parallel with the emergence of independent finger movements (Lawrence and Hopkins, 1976) and suppression of the primitive reflexes (Palmer *et al.*, 1983). Myelination of the corticospinal pathways, however, is not complete until 2 yrs of age (Yakovlev and Lecours, 1967; Rorke and Riggs, 1969). If a lesion of the corticospinal pathways occurred during this period of development then the pattern of connectivity of these pathways or their presynaptic inputs might be altered. A lesion could disrupt the mechanism(s), for example, responsible for axonal elimination (Cox *et al.*, 1989; Humphrey and O'Donoghue, 1989) or the signals generated by the target regions (Kuang and Kalil, 1989) that guide the corticospinal tract to the appropriate groups of motoneurons and interneurons, thus determining its specificity.

In conclusion, the present study provides evidence that in humans, as in animals, lesions of the immature brain and corticospinal tract result in altered corticospinal projections. In CP the altered projections appear to be directed equally to the motoneurons of both agonist and antagonist ankle muscles. This may explain why voluntary movements in these subjects are often disrupted by cocontraction of flexor and extensor muscles.

ACKNOWLEDGEMENTS

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REFERENCES

AMASSIAN VE, ROSS RJ (1978) Electrophysiological correlates of the developing sensorimotor system. *Journal de Physiologie, Paris*, **74**, 185–201.

AMASSIAN VE, STEWART M, QUIRK GJ, ROSENTHAL JL (1987) Physiological basis of motor effects of a transient stimulus to cerebral cortex. *Neurosurgery*, **20**, 74–93.

AMASSIAN VE, CRACCO RQ, MACCABEE PJ (1988) Basic mechanisms of magnetic coil excitation of nervous system in humans and monkeys and their applications. *Proceedings of a Special Symposium on Maturing Technologies and Emerging Horizons in Biomedical Engineering IEEE.* New Orleans, November, pp. 10–17.

ASANUMA H, ZARZECKI P, JANKOWSKA E, HONGO T, MARCUS S (1979) Projection of individual pyramidal tract neurons to lumbar motor nuclei of the monkey *Experimental Brain Research*, **34**, 73–89.

ASHBY P, ZILM D (1982) Characteristics of postsynaptic potentials produced in single human motoneurons by homonymous group I volleys. *Experimental Brain Research*, **47**, 41–48.

BARABAS G, TAFT LT (1986) The early signs and differential diagnosis of cerebral palsy. *Pediatric Annals*, **15**, 203–214.

BARKER AT, FREESTON IL, JALINOUS R, JARRATT JA (1987) Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery*, **20**, 100–109.

BAX MCO (1964) Terminology and classification of cerebral palsy. *Developmental Medicine and Child Neurology*, **6**, 295–297.

BERBRAYER D, ASHBY P (1990) Reciprocal inhibition in cerebral palsy. *Neurology, Cleveland*, **40**, 653–656.

BREGMAN BS, GOLDBERGER ME (1983) Infant lesion effect: III. Anatomical correlates of sparing and recovery of function after spinal cord damage in newborn and adult cats. *Developmental Brain Research*, **9**, 137–154.

BROUWER B, ASHBY P, MIDRONI G (1989) Excitability of corticospinal neurons during tonic muscle contractions in man. *Experimental Brain Research*, **74**, 649–652.

BROUWER B, ASHBY P (1990*a*) Do injuries to the developing human brain alter corticospinal projections? *Neuroscience Letters*, **108**, 225–230.

Brouwer B, Ashby P (1990*b*) Corticospinal projections to upper and lower limb spinal motoneurons in man. *Electroencephalography and Clinical Neurophysiology*, **76**, 509–519.

Bruce IC, Tatton WG (1981) Descending projections to the cervical spinal cord in the developing kitten. *Neuroscience Letters*, **25**, 227–231.

Bugaresti JM, Brouwer B, Ashby P (1990) Corticospinal projections to lower limb spinal motoneurons in incomplete spinal cord injured patients. *Proceedings of American Spinal Injury Association*, Orlando, FL, May 1–3.

Cope TC, Fetz EE, Matsumura M (1987) Cross-correlation assessment of synaptic strength of single 1a fibre connections with triceps surae motoneurones in cats. *Journal of Physiology, London*, **390**, 161–188.

Cowan JMA, Day BL, Marsden C, Rothwell JC (1986) The effect of percutaneous motor cortex stimulation on H reflexes in muscles of the arm and leg in intact man. *Journal of Physiology, London*, **377**, 333–347.

Cox MTS, O'Donoghue DL, Humphrey DR (1989) Growth, elimination and myelination of corticospinal axons in the postnatal rat. *Society for Neuroscience Abstracts*, **15**, 68.

Day BL, Dressler D, Maertens de Noordhout A, Marsden CD, Nakashima K, Rothwell JC *et al.* (1989) Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology, London*, **412**, 449–473.

Dietz V, Berger W (1983) Normal and impaired regulation of muscle stiffness in gait: a new hypothesis about muscle hypertonia. *Experimental Neurology*, **79**, 680–687.

Edgley SA, Eyre JA, Lemon RN, Miller JSG (1989) Direct activation of corticospinal neurones by electromagnetic stimulation in anaesthetized and conscious monkeys. *Journal of Physiology, London*, **414**, 8*P*.

Edgley SA, Eyre JA, Lemon RN, Miller S (1990) At what level is the corticospinal pathway excited by electromagnetic and percutaneous electrical stimulation of the brain? Evidence from the anaesthetized macaque monkey. *Journal of Physiology, London*, **420**, 47*P*.

Fetz EE, Gustafsson B (1983) Relation between shapes of post-synaptic potentials and changes in firing probability of cat motoneurones. *Journal of Physiology, London*, **341**, 387–410.

Gómez-Pinilla F, Villablanca JR, Sonnier BJ, Levine MS (1986) Reorganization of pericruciate cortical projections to the spinal cord and dorsal column nuclei after neonatal or adult cerebral hemispherectomy in cats. *Brain Research, Amsterdam*, **385**, 343–355.

Gorman ALF (1966) Differential patterns of activation of the pyramidal system elicited by surface anodal and cathodal cortical stimulation. *Journal of Neurophysiology*, **29**, 547–564.

Gottlieb GL, Myklebust BM, Penn RD, Agarwal GC (1982) Reciprocal excitation of muscle antagonists by the primary afferent pathway. *Experimental Brain Research*, **46**, 454–456.

Hallett M, Alvarez N (1983) Attempted rapid elbow flexion movements in patients with athetosis. *Journal of Neurology, Neurosurgery and Psychiatry*, **46**, 745–750.

Hess CW, Mills KR, Murray NMF (1987) Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology, London*, **388**, 397–419.

Humphrey DR, O'Donoghue DL (1989) Postnatal changes in the number, density and distribution of corticospinal neurons in the rat. *Society for Neuroscience Abstracts*, **15**, 69.

Humphrey T (1960) The development of the pyramidal tracts in human fetuses, correlated with cortical differentiation. In: *Structure and Function of the Cerebral Cortex.* Edited by D. B. Tower and J. P. Schadé. Amsterdam: Elsevier, pp. 93–103.

Ingram TTS (1964) *Paediatric Aspects of Cerebral Palsy.* Edinburgh: E. and S. Livingstone.

Jankowska E, Padel Y, Tanaka R (1976) Disynaptic inhibition of spinal motoneurones from the motor cortex in the monkey. *Journal of Physiology, London*, **258**, 467–487.

Jasper HH (1958) Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology*, **10**, 370–375.

Kuang RZ, Kalil K (1989) Sprouting of corticospinal fibers into denervated contralateral spinal cord reveals specificity of new axon arbors. *Society for Neuroscience Abstracts*, **15**, 92.

Lawrence DG, Hopkins DA (1976) The development of motor control in the rhesus monkey: evidence concerning the role of corticomotoneuronal connections. *Brain*, **99**, 235–254.

Mailis A, Ashby P (1990) Alterations in group la projections to motoneurons following spinal lesions in humans. *Journal of Neurophysiology*, **64**, 637–647.

Mao CC, Ashby P, Wang M, McCrea D (1984) Synaptic connections from large muscle afferents to the motoneurons of various leg muscles in man. *Experimental Brain Research*, **56**, 341–350.

Midroni G, Ashby P (1989) How synaptic noise may affect cross-correlations. *Journal of Neuroscience Methods*, **27**, 1–12.

Milner-Brown HS, Penn RD (1979) Pathophysiological mechanisms in cerebral palsy. *Journal of Neurology, Neurosurgery and Psychiatry*, **42**, 606–618.

Myklebust BM, Gottlieb GL, Penn RD, Agarwal GC (1982) Reciprocal excitation of antagonistic muscles as a differentiating feature in spasticity. *Annals of Neurology*, **12**, 367–374.

Palmer FB, Shapiro BK, Wachtel RC, Capute AJ (1983) Primitive reflex profile. In: *Comprehensive Management of Cerebral Palsy*. Edited by G. H. Thompson, I. L. Rubin and R. M. Bilenker. New York and London: Grune and Stratton, pp. 171–179.

Rorke LB, Riggs HE (1969) *Myelination of the Brain in the Newborn*. Philadelphia: J. B. Lippincott.

Theriault E, Tatton WG (1989) Postnatal redistribution of pericruciate motor cortical projections within the kitten spinal cord. *Developmental Brain Research*, **45**, 219–237.

Tolbert DL, Der T (1987) Redirected growth of pyramidal tract axons following neonatal pyramidotomy in cats. *Journal of Comparative Neurology*, **260**, 299–311.

Villablanca JR, Olmstead CE, Sonnier BJ, McAllister JP, Gomez F (1982) Evidence for a crossed corticorubral projection in cats with one cerebral hemisphere removed neonatally. *Neuroscience Letters*, **33**, 241–246.

Villablanca JR, Burgess JW, Olmstead CE (1986) Recovery of function after neonatal or adult hemispherectomy in cats: I. Time course, movement, posture and sensorimotor tests. *Behavioural Brain Research*, **19**, 205–226.

Wise SP, Hendry SHC, Jones EG (1977) Prenatal development of sensorimotor cortical projections in cats. *Brain Research, Amsterdam*, **138**, 538–544.

Yakovlev PI, Lecours A-R (1967) The myelogenetic cycles of regional maturation of the brain. In: *Regional Development of the Brain in Early Life*. Edited by A. Minkowski. Oxford: Blackwell, pp. 3–70.

Yang BJ, Brouwer B, Hajek VE, Ashby P (1990) Magnetic stimulation of short latency corticospinal pathways following unilateral cerebral infarction. *Canadian Journal of Rehabilitation*, **4**, 39–45.

Zarola F, Caramia MD, Paradiso C, Mariorenzi R, Martino G, Traversa R *et al.* (1989) Single fibre motor evoked potentials to brain, spinal roots and nerve stimulation. Comparisons of the 'central' and 'peripheral' response jitter to magnetic and electric stimuli. *Brain Research, Amsterdam*, **495**, 217–224.

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TRANSCORTICAL APHASIA

IMPORTANCE OF THE NONSPEECH DOMINANT HEMISPHERE IN LANGUAGE REPETITION

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SUMMARY

While a relative preservation of repetition in acute transcortical aphasia (TA) has usually been associated with the functional integrity of the speech dominant (left) perisylvian area, recent amytal data (Bando *et al.*, 1986) have suggested a fundamental role of the nondominant (right) hemisphere in language repetition. The neuroradiological correlates of repetition were studied in a consecutive series of 21 patients with acute TA. A similar frequency of either perisylvian or extraperisylvian pathology was found. In 2 patients with perisylvian pathology, the injection of amytal in the hemisphere contralateral to the lesion abolished repetition. Positron emission tomography (PET) in another patient revealed marked hypometabolism over the entire left cortical mantle ipsilateral to a basal ganglia lesion, suggesting that preserved repetition was carried out by right hemisphere structures. This was confirmed in a second patient with left extraperisylvian pathology, in whom a second lesion in the right hemisphere resulted in impaired repetition. These findings suggest that the spared contralateral hemisphere may subserve residual repetition in some transcortical aphasic patients with a lesion within or outside the speech-dominant perisylvian area.

INTRODUCTION

Transcortical aphasia (TA) is characterized by a relative preservation of sentence repetition in the context of severe disturbances in the comprehension and/or production of oral language (Wernicke, 1885–1886; Albert *et al.*, 1981; Rubens and Kertesz, 1983). Different types of TA have been described.

Transcortical motor aphasia (TMA) is characterized by transient mutism followed by difficulty in language initiation and reduced verbal output. Patients show echolalic repetition, normal auditory comprehension and adequate object naming. TMA has been reported after a lesion outside Broca's area, either in the white matter anterolateral to the left frontal horn (Damasio, 1981; Freedman *et al.*, 1984) or in the mesial left frontal lobe involving the supplementary motor area (Rubens, 1975; Masdeu *et al.*, 1978; Alexander and Schmitt, 1980; Damasio and Van Hoesen, 1980; Ross, 1980; Naeser *et al.*, 1981; Freedman *et al.*, 1984).

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Transcortical sensory aphasia (TSA) is characterized by fluent but semantically irrelevant and empty spontaneous speech, and impairment both of auditory comprehension and object naming in the presence of normal repetition. TSA often results from diffuse brain pathology (e.g., Alzheimer's disease; Cummings *et al.*, 1985) or focal lesions in the left temporo-parieto-occipital junction, posterior to Wernicke's area (Kertesz *et al.*, 1982), or thalamic haemorrhages (Cappa and Vignolo, 1979).

Mixed transcortical aphasia (MTA) is characterized by a severely reduced verbal output and impaired auditory comprehension, in the presence of echolalic repetition and automatic completion of open-ended sentences. MTA is associated with diffuse (Whitaker, 1976; Mehler, 1988) or multifocal brain pathology (Geschwind *et al.*, 1968; Assal *et al.*, 1983); two simultaneous but independent vascular lesions (one anterior, in the precentral-central cortex, and the other, in the temporo-occipital cortex) (Bogousslavsky *et al.*, 1988); or single vascular lesions in the left frontoparietal region (Ross, 1980; Speedie *et al.*, 1984).

It has classically been considered that in TA, repetition is carried out by the spared left perisylvian area (i.e., Heschl's gyrus, Wernicke's area, Broca's area, inferior left precentral gyrus, and their interconnections) (Lichtheim, 1885; Wernicke, 1885–1886; Goldstein, 1948; Geschwind, 1965; Rubens and Kertesz, 1983). In support, several neuropathological (Geschwind *et al.*, 1968; Assal *et al.*, 1983) and radiological studies (Kertesz *et al.*, 1977; Naeser and Hayward, 1978) showed that TA resulted from acute brain lesions surrounding the speech area, thus potentially disconnecting the intact perisylvian language zone from the peripheral brain areas that may be essential for meaning and intention (Lichtheim, 1885).

Over the years, the model of 'isolation' of the speech area (Goldstein, 1948; Geschwind, 1965) has been considered a likely model to explain the preservation of repetition in TA. Alternative mechanisms, however, have also been suggested. Early authors (Hübner, 1889; Bastian, 1897; Vix, 1910; Henschen, 1920–1922; Goldstein, 1948) reported TA after lesions that partially involved the left speech area, and it was Bastian who in 1897 first suggested that partial damage to the major speech centres would impair language expression or comprehension but would spare repetition by increasing the threshold of speech area to externally generated stimuli. Other authors (Niessl von Mayendorf, 1911; Stengel, 1936, 1947) suggested that repetition in TA is carried out by either the verbal nondominant (right) hemisphere, or by joint activity of noninvolved left hemisphere structures and the intact right hemisphere (Mohr, 1973; Brown, 1975; Rubens, 1975). Indirect support of the importance of the contralateral (spared) hemisphere in language repetition was provided by several patients (Brown, 1975; Selnes *et al.*, 1982, 1985; Kapur and Dunkley, 1984; Basso *et al.*, 1985; Bolla-Wilson *et al.*, 1985; Reinvang, 1987; Trojano *et al.*, 1988; Alexander *et al.*, 1989), who despite having extensive damage to the central language zone, showed a relative preservation of repetition.

While the above mechanisms have been suggested to explain the preservation of repetition in TA, a clinical-neuroradiological study, including a consecutive series of patients with the three clinically established varieties of TA (TMA, TSA and MTA), has never been undertaken. For the present study, we have examined a consecutive series of patients admitted to a neurology unit after an acute hemisphere lesion. Our main aim was to examine the neuroradiological correlates of TA and the mechanism of repetition in TA using more specific testing methods of brain function such as positron emission tomography (PET) and amytal tests.

METHODS

Patients

Patients included in this study were selected from 104 consecutive admissions to the Institute of Neurological Research, Buenos Aires, Argentina, for the evaluation and treatment of language impairments after brain lesions, and from 10 consecutive admissions to the University of Maryland Hospital for the treatment of acute infarction or intracerebral haemorrhage. Patients included in this study met the following criteria: (1) presence of an acute focal brain lesion in the absence of previous brain injury, and (2) less than 2 mos of evolution after the brain lesion.

Language examination

Handedness was assessed using the 6-item questionnaire of the Western Aphasia Battery (WAB) (Kertesz, 1982). Patients were considered right-handers if they reported the use of their right hand in all 6 items. For those patients with a history of switched handwriting (from left to right hand), consideration of hand dominance was based on the initial hand preference. Family history of left-handedness was considered positive when at least one first degree relative was left-handed or ambidextrous.

All the aphasic patients included in this study were assessed with the WAB. The oral subtests (spontaneous speech, comprehension, repetition, and naming) as well as reading, writing and nonverbal subtests (drawing, block design, calculation and Raven's Coloured Progressive Matrices) were given to every patient.

Classification of the different types of TA were made using the WAB taxonomic criteria, which are based on the Fluency, Comprehension and Repetition subtests scores (Transcortical motor aphasia: fluency score ≤ 4, Comprehension score ≥ 4, Repetition score ≥ 8; Transcortical sensory aphasia: Fluency score ≥ 5, Comprehension score < 7, Repetition score ≥ 8; Mixed transcortical aphasia: Fluency score < 4, Comprehension score < 4, Repetition score ≥ 5).

Neuroradiological examination

CT scans (GE CT/8800 and GE CT/MAX) and/or MRI scans (1.5 T, Phillips Gyroscan) were obtained for every patient 2–6 wks after the stroke: 5 mm slices parallel to the canthomeatal line were obtained.

CT and MRI scans were read by one of us (S.E.S.) who was blind to the clinical findings. The damaged area was mapped using an atlas (Matsui and Hirano, 1978), and localized in specific brain areas using the method of Levine and Grek (1984). Lesion areas (expressed as the percentage of total brain area) were calculated from the ratio of the cross-sectional area of the lesion on the CT/MRI scan slice where the lesion was present, divided by the cross-sectional area of the whole brain on the same slice (Starkstein *et al.*, 1988). If lesions were present in more than one slice, an average was obtained. All the area measurements were carried out using an image analysis system (IBM/Bioquant System IV, R and M Biometrics, Nashville, TN).

Based on neuroradiological findings, patients were divided in 2 groups. (1) Perisylvian group (PS): patients had lesions involving one or more of the following brain areas: Heschl's gyrus (primary auditory cortex), Wernicke's area (posterior-superior temporal lobe), inferior parietal lobe (infrasylvian supramarginal gyrus), Broca's area (inferior frontal gyrus), foot of the primary motor area (precentral gyrus), insular cortex, claustrum, or white matter tracts connecting these structures (arcuate fasciculus, extreme capsule, and external capsule); (2) Extraperisylvian group (EPS): patients had lesions located exclusively outside the perisylvian speech area (i.e., temporo-occipital junction, superior parietal lobe, supplementary motor area, thalamus, or basal ganglia).

Measurement of cerebral asymmetries. The cerebral hemispheres were divided by a line extending from the anterior falx-inner table junction, to the posterior falx-inner table junction. Perpendicular lines were then drawn from the midsaggital line to the inner table of the skull on the right and left hemispheres at 0.90 (frontal) and 0.16 (occipital) of the anteroposterior diameter (Dewan *et al.*, 1987). The areas of the left and right frontal and occipital regions, as well as the area of the whole brain at the same level, were measured (inter-rater reliability r = 0.99), and an Asymmetry Index (AI) was calculated using the following formula (Luchins and Meltzer, 1983):

$$\mathrm{AI} = \frac{\text{Right area} - \text{Left area}}{\text{Right area} + \text{Left area}} \times 100$$

Other studies. Several patients (described below) underwent complementary studies (*see* Appendices 1, 2) such as intracarotid amytal testing (2 patients), and 18 fluorodeoxyglucose (FDG) PET-scan study (1 patient).

Statistical analysis

Statistical analysis was performed using means and SDs, Student's t test (2-tailed), and analysis of variance (ANOVA). Frequency distributions were analysed using a χ^2 test with a Yates' modification for expected cell sizes below 5.

RESULTS

Eighteen of the 104 (17%) consecutively studied aphasic patients at the Institute of Neurological Research showed TA. The other 3 patients were selected from a consecutive series of 10 stroke patients examined at the University of Maryland. While 9 patients (43%) had perisylvian lesions (PS group), 12 patients (57%) had lesions limited to extraperisylvian areas (EPS group).

Within the PS group, 5 patients (55%) showed a TSA, 3 patients (33%) showed a MTA, and 1 patient (11%) showed a TMA. Within the EPS group, 9 patients (75%) showed a TSA, 2 patients (16%) showed a TMA, and 1 patient (8%) showed a MTA. A hypothesis of unequal frequency of type of TA based on the presence or absence of perisylvian damage was not statistically substantiated ($\chi^2 = 0.93$, df = 2, $P = 0.62$).

Patients

Background information revealed no significant between-group differences in age (yrs) (mean ± SD): PS: 56.4 ± 13.2, EPS: 64.9 ± 9.2, sex (% females): PS: 33%, EPS 58%, education (yrs) (mean ± SD): PS: 14.3 ± 3.6, EPS: 11.6 ± 3.9, handedness (% right-handed): PS: 77, EPS: 83, family history of left-handedness (% positive): PS 33, EPS: 8.3, and time since stroke (mean days): PS: 17, EPS: 17.

Neurological findings

No significant between-group differences were observed in motor deficits (PS: 75%, EPS: 75%), sensory deficits (PS: 62%, EPS: 67%), visual field deficits (PS: 44%, EPS: 54%), and neglect (PS: 55%, EPS: 91%).

Language findings

Since the scoring scales differed for each subtest, a Z score transformation of WAB subtest scores was carried out. A two-way ANOVA (factor 1: group (PS vs EPS), factor 2: WAB subtests) showed a significant group effect ($F = 12.7$, df = 1,190, $P < 0.01$) (the PS group showed significantly lower WAB scores (i.e., more severe aphasia) than the EPS group), but no significant group by WAB subtest interaction (i.e., the profile of language deficits was not significantly different between the 2 groups (Tables 1 and 2).

TABLE 1 RESULTS OF THE WESTERN APHASIA BATTERY—PERISYLVIAN GROUP

Case	*IC*	*F*	*Y/N*	*AWR*	*SQ*	*R*	*ON*	*WF*	*SC*	*RS*	*AQ*	*Aphasia type*
1	8	7	48	38	44	9.8	30	0	4	6	70.6	TSA
2	4	8	48	53	29	8.4	45	5	2	8	65.8	TSA
3	4	7	51	8	6	8.4	3	0	2	2	43.2	TSA
4	4	7	54	46	8	8.9	22	0	6	4	57.0	TSA
5	9	8	39	50	16	9.8	60	6	6	10	80.4	TSA
6	0	0	26	26	0	7.0	12	0	0	0	26.8	MTA
7	2	0	57	32	8	7.9	9	0	4	4	32.8	MTA
8	3	0	52	20	2	5.2	7	0	6	0	26.4	MTA
9	6	4	54	54	68	10.0	38	1	8	8	68.6	TMA
GM	4.4	4.6	47.6	36.3	19.9	8.3	25.1	1.3	4.2	4.6	52.5	
SD	(2.8)	(3.6)	(9.6)	(16.0)	(23.0)	(15.4)	(19.5)	(2.3)	(2.5)	(3.6)	(21.0)	

IC information content; F = fluency, Y/N = yes/no questions; AWR = auditory word recognition; SQ = sequential commands; R = repetition; ON = object naming; WF = word fluency; SC = sentence completion; RS = response speech; AQ = aphasia quotient; GM = group mean; SD = standard deviation, TSA = transcortical sensory aphasia; MTA = mixed transcortical aphasia; TMA = transcortical motor aphasia.

TABLE 2. RESULTS OF THE WESTERN APHASIA BATTERY—EXTRAPERISYLVIAN GROUP

Case	*IC*	*F*	*Y/N*	*AWR*	*SQ*	*R*	*ON*	*WF*	*SC*	*RS*	*AQ*	*Aphasia type*
10	5	6	45	54	14	8.0	38	5	6	6	60.6	TSA
11	4	7	39	42	12	8.4	20	1	6	6	54.6	TSA
12	4	7	51	54	18	8.2	15	3	6	4	55.4	TSA
13	6	8	50	50	30	8.0	51	6	10	8	72.0	TSA
14	9	9	48	48	36	9.6	58	5	8	8	84.0	TSA
15	8	9	51	41	10	9.4	58	2	8	10	78.6	TSA
16	8	9	51	50	16	9.8	60	2	10	8	81.2	TSA
17	9	10	48	44	22	9.0	60	5	6	8	82.2	TSA
18	6	5	51	41	34	8.7	58	3	10	10	68.2	TSA
19	0	0	45	34	4	8.0	0	0	0	0	24.0	MTA
20	4	0	12	2	6	10.0	3	4	6	10	56.6	MTA
21	6	2	60	57	60	8.6	41	5	10	10	64.0	TMA
GM	5.7	6.0	42.2	42.1	21.8	8.8	38.5	3.4	7.1	7.5	63.2	
SD	(2.8)	(3.6)	(14.1)	(14.1)	(15.9)	(7.3)	(23.0)	(1.8)	(2.8)	(2.9)	(18.8)	

Abbreviations as in Table 1.

Further testing of language abilities

In order to investigate more closely the mechanism subserving repetition, the following tests of language processing were carried out.

Frequency of phonological and semantic paraphasias. The amount of phonological and semantic errors produced by the PS and EPS groups during the WAB object-naming test were examined in all patients with TA. While the EPS group produced significantly more semantic errors ($\chi^2 = 8.10$, df = 1, $P < 0.01$), there were no significant between-group differences in the frequency of phonological errors ($\chi^2 = 1.28$, df 1, P = n.s.).

Spontaneous correction of syntactic and semantic errors. The ability to correct syntactic and semantic errors during the repetition of sentences with grammatical or semantic errors (Berndt *et al.*, 1987) was examined in a subsample of 9 patients with transcortical sensory aphasia (PS group, n = 4, EPS group, n = 5). There were 10 deviant sentences that violated minor syntactic rules, such as errors of number agreement (i.e., 'The navigators leaves the boat'), or pronoun usage (i.e., 'He gave she a present'), and 10 sentences with semantic errors (i.e., 'Cats have six legs'). Six of 9 patients could correct syntactic errors spontaneously; 4 of them (Cases 14, 15, 16, 17) had extraperisylvian involvement, whereas the other 2 patients, who also showed good syntactic processing (Cases 1, 2) had perisylvian damage. The remaining 3 patients did not correct syntactic errors; 2 of them (Cases 3, 5) had extensive perisylvian involvement, and the other patient (Case 12) had extraperisylvian damage. None of these 9 patients with TSA was able to detect semantic errors, and they repeated verbatim these semantically anomalous sentences.

Repetition of nonwords. The 9 patients with TSA were also asked to repeat a list of 20 auditorily presented nonwords. These nonwords were orthographically regular, with a length ranging from 4 to 8 letters (e.g., dero, solchato). All 9 patients could repeat nonwords flawlessly.

Neuroradiological findings

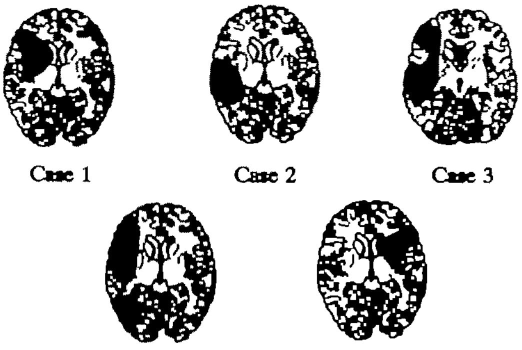
Perisylvian group (fig. 1)

Two of the 5 patients with TSA (Cases 1, 5) showed ischaemic infarct involving the anterior perisylvian area (Broca's area, inferior precentral gyrus, and insula) with extension into the subjacent basal ganglia and internal capsule. Case 5 (a left-hander) had a right hemisphere lesion. One of the remaining 3 patients (Case 3) had a large ischaemic infarct involving almost the whole left perisylvian area, a second patient (Case 4) had two separate ischaemic infarcts involving the left frontotemporal cortex and the left temporoparietal cortex, and the remaining patient (Case 2) had a large haemorrhagic metastatic tumour involving the left posterior speech area (Heschl's gyrus, Wernicke's area, and the infrasylvian supramarginal gyrus), with only mild peritumoural oedema. One of the 3 patients with a MTA (Case 8) showed a large ischaemic infarct involving the whole left perisylvian speech area (fronto-temporo-parietal cortex), a second patient (Case 6) had a left ischaemic infarct involving the frontoparietal operculum, corona radiata, insula, and the supramarginal gyrus, and the third patient (Case 7) had 2 simultaneous left ischaemic infarcts, one involving Broca's area, the inferior precentral gyrus, insula, putamen, and the anterior corona radiata, and the other the posterior temporal, occipital and parietal lobes. The only patient with a TMA (Case 9) had an ischaemic infarct restricted to Broca's area and the adjacent inferior precentral gyrus.

Extraperisylvian group (fig. 2)

Five of the 9 patients with TSA (Cases 10, 13, 14, 15, 17) showed left posterior cortical lesions (2 haemorrhagic and 1 ischaemic inferior and/or superior parietal lobe lesions, 1 temporo-parieto-occipital junction haemorrhage, and 1 temporo-occipital cortical ischaemic infarct), 2 patients (Cases 11, 12) had left putaminal haemorrhages (1 patient showed mild extension into the nearby temporal isthmus and internal capsule),

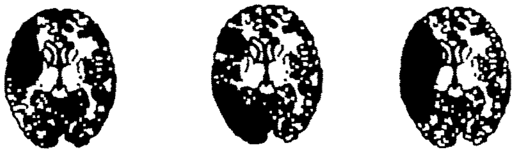
Transcortical sensory aphasia



Case 1 Case 2 Case 3

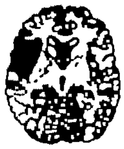
Case 4 Case 5

Mixed transcortical aphasia



Case 6 Case 7 Case 8

Transcortical motor aphasia



Case 9

Fig. 1. *PS group*. Schematic representation of lesion location in cross-sectional slices.

1 patient (Case 16) had a large left parietofrontal (centrum semiovale) haemorrhage, and the remaining patient (Case 18) had a left dorsolateral frontal ischaemic infarct.

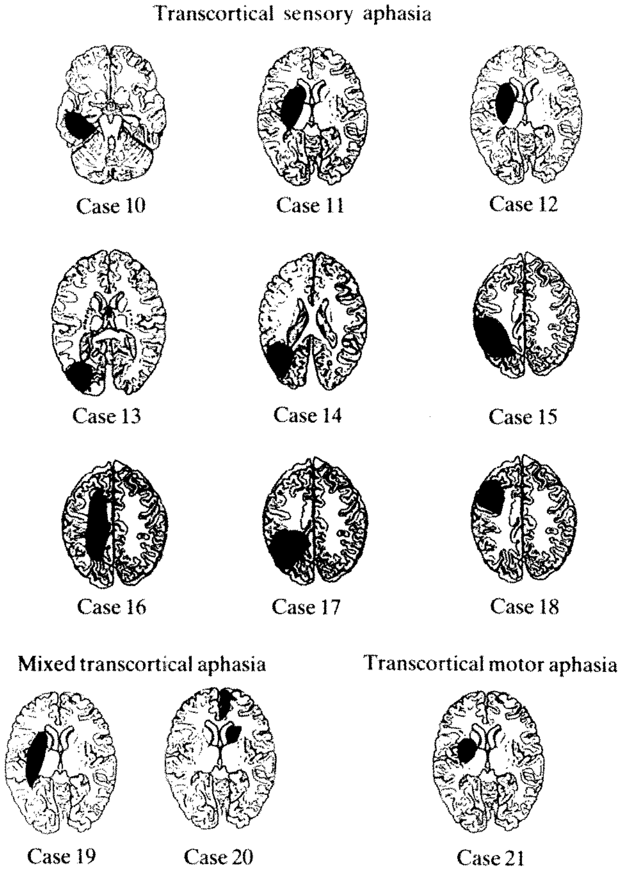
One of the 2 patients with a MTA (Case 19) showed a large left putaminal haemorrhage with extension into the nearby internal capsule and temporal isthmus, while the other patient (Case 20) (a left-hander) showed a right hemisphere ischaemic infarct involving the head of the caudate, anterior limb of the internal capsule, anterior putamen, anterior cingulate gyrus, and superior frontoparietal white matter.

The only patient with a TMA (Case 21) showed a haemorrhage restricted to the anterior portion of the left putamen.

Cerebral asymmetries and lesion volume

A two-way ANOVA (*factor 1*; group (PS vs EPS), *factor 2*: region (frontal vs occipital) showed no significant groups effects (F (1,19) = 0.72, P = n.s.), and no significant interaction (F (1,19) = 2.25, P = n.s.). Both groups showed larger right than left frontal areas, and larger left than right occipital areas.

No significant between-group differences were observed in lesion volume (t = 0.83, df = 19, P = 0.41).



Transcortical sensory aphasia

Case 10 Case 11 Case 12

Case 13 Case 14 Case 15

Case 16 Case 17 Case 18

Mixed transcortical aphasia

Case 19 Case 20

Transcortical motor aphasia

Case 21

FIG. 2. *EPS group*. Schematic representation of lesion location in cross-sectional slices.

ILLUSTRATIVE CASE REPORTS

Perisylvian group

Case 1. Transcortical sensory aphasia

This patient was 62 yr-old right-handed woman, who was admitted because of a fluent aphasia and right-sided weakness. On examination she had a mild right hemiparesis. Her spontaneous speech was mildly dysarthric, monotonous and hypophonic, and fluency was frequently disrupted by word-finding pauses. The patient could only generate semantically empty, circumlocutory and perseverative short phrases. While phonological paraphasias were abundant, semantic paraphasias and neologistic jargon were rare. On some occasions, fully-formed sentences were produced in response to specific questions. Series speech and singing were preserved and were remarkably better than oral expression. On both the WAB (*see* Table 1) and the Token Tests, auditory comprehension was moderately impaired (WAB comprehension subtest; 6.5/10, Token Test: 16/62). The patient could repeat words, nonwords and nonverbal sounds flawlessly. On a repetition test composed of semantically anomalous/ungrammatical sentences (Berndt *et al.*, 1987), the patient corrected 50% of syntactic errors but none of the semantic errors. During the testing session she echoed most of the examiner's question. These echoes were of normal rhythm but devoid of intonation. While object-naming and word fluency were severely impaired, reading comprehension of sentences on the WAB was moderately impaired (20/40). She also showed a moderate buccofacial apraxia and a left arm ideomotor apraxia. On dichotic listening (Damasio and Damasio, 1979) she showed a left ear 'paradoxic' extinction (0/110) and a normal right ear performance (104/110). Serial CT and MRI scans showed an ischaemic infarction involving the left anterior perisylvian area (fig. 3).

Amytal test. After a right carotid amytal injection the patient had a transient clouding of consciousness (which lasted for 20 s), followed by a global aphasia. The patient remained mute for 90 s, and could not repeat simple words or name common objects. Auditory comprehension for simple questions was severely impaired. A left carotid injection could not be carried out.

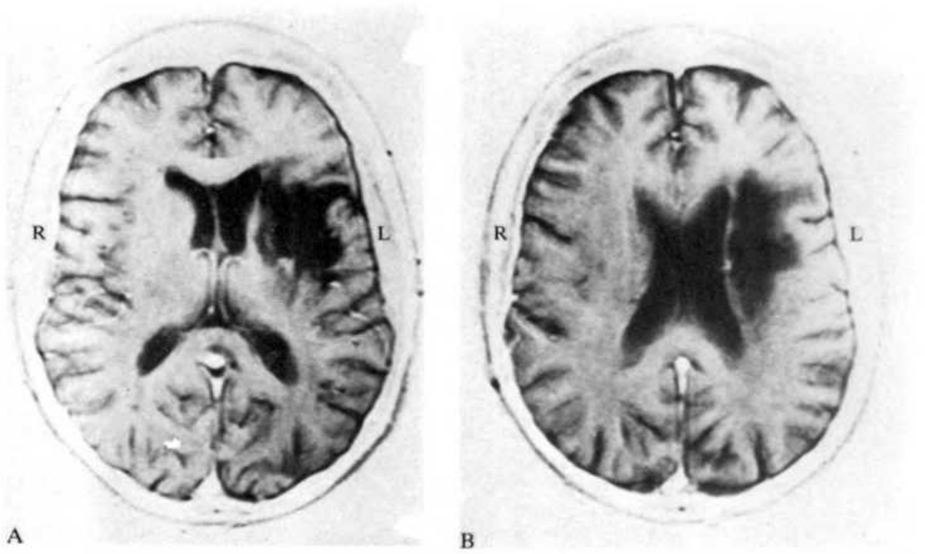


FIG. 3. MRI scan (inverted T_2-weighted image) showing a left hemisphere infarct involving the head of the caudate nucleus, the anterior limb and genu of the internal capsule, and the putamen, A, extending laterally into the external capsule, claustrum, extreme capsule, insula, and the posterior-inferior frontal cortex (Broca's area) and B, rostrally into the corona radiata.

Case 5. Transcortical sensory aphasia

This patient was a 56-yr-old nonfamilial left-handed man, who suddenly became unable to understand his wife's speech. On admission, he was alert but was apathetic and unconcerned. He had a mild left hemiparesis, left hemispatial neglect, motor impersistence, impaired right-left discrimination, and spatial disorientation. His spontaneous speech was fluent, with normal articulation and prosody. Although sentences were short and often contaminated by echolalia and perseverations, they conveyed a meaningful message. There were no phonological semantic or neologistic paraphasias. Series speech and the recitation of days of the week were flawless. Language comprehension was worse than oral expression. During the testing session, a remarkable fluctuation in the patient's comprehension abilities was noted (i.e., while he could not understand some simple questions, he could answer some of the more complex ones). He scored abnormally low on the comprehension subtests of the WAB (*see* Table 1), and in the Token Test (35/62). He repeatedly echoed the initial portion of most questions and automatically repeated entire sentences. Repetition of words, sentences, nonwords and nonverbal sounds was intact. On a repetition test composed of semantically anomalous/ungrammatical sentences (Berndt *et al.*, 1987), he was able to repeat all the sentences correctly, but his performance had a 'parrot-like' pattern, and he was unable to correct either syntactic (0/10) or semantic (0/10) errors. Except for a reduced word list generation (animal naming: 6 words in 1 min), naming was largely preserved. He achieved normal scores on the Boston Naming Test (54/60), naming actions (10/10), parts of a car (8/10), body parts (9/10), colours (10/10), fruits (9/10) and letters

(20/20). Tactile and auditory naming were also intact, and he performed flawlessly in written confrontation naming (20/20). While reading aloud was normal, he had impaired reading comprehension of the sentences of the WAB (16/40). He could write normally with either hand. There was no evidence of buccofacial apraxia or limb apraxia. On dichotic listening (Damasio and Damasio, 1979) the patient showed complete left ear extinction (3/110) and normal right ear performance (107/110). Serial CT and MRI scans showed a large ischaemic infarct involving the right anterior perisylvian area (fig. 4).

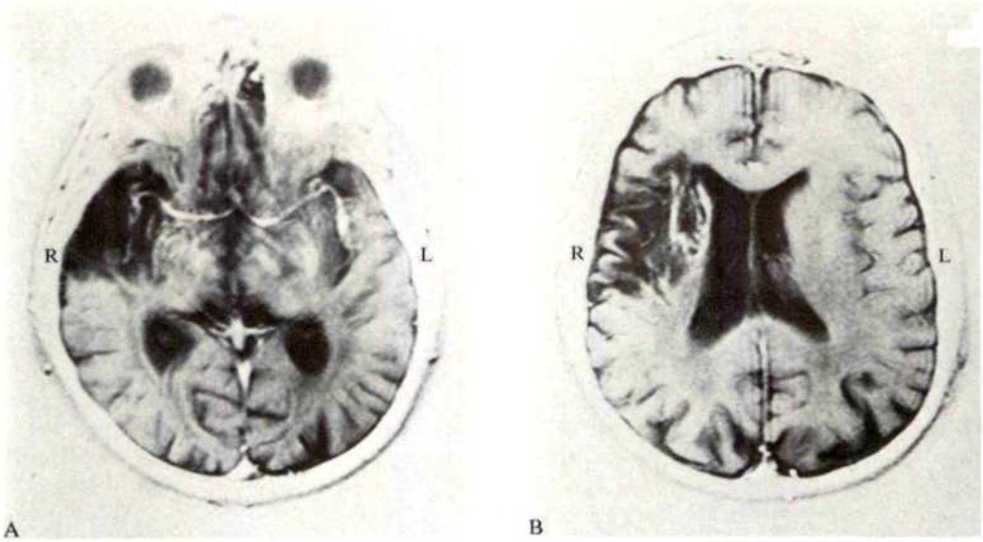


FIG. 4. MRI scan (inverted T_2-weighted image) showing a large right hemisphere infarct involving (A), the anterolateral temporal lobe (including Heschl's gyrus), and (B), the posterior-inferior frontal cortex, extending into the extreme capsule, claustrum, external capsule, insula, putamen, internal capsule, head of the caudate nucleus and the anterior two-thirds of the corona radiata.

Amytal test. A right carotid injection did not change the pattern of language impairment. During the period of effective narcosis, the patient remained fully alert and spoke clearly, with fluent and meaningful sentences. He was able to name 10 common objects and to repeat 5 four-word sentences (e.g., 'John drives the car') flawlessly. Auditory comprehension remained unchanged (i.e., he could understand simple questions but not complex material).

A left carotid injection produced a transient loss of consciousness (35 s) followed by a global aphasia, which lasted 2 min. During this period, the patient was totally unable to phonate or move his tongue and lips, either on verbal command or to imitation, rendering repetition and object-naming impossible to test. The patient could not understand simple questions or one-step commands.

Extraperisylvian group

Case 12. Transcortical sensory aphasia

This 75-yr-old right-handed woman was admitted to the emergency room after having fallen in the street. On admission she was lethargic, rousable, but slow to respond. There was a left gaze preference and a decreased blink to threat to right-sided stimuli. She also showed right auditory and tactile alloaesthesia, right hemiplegia and right hemisensory loss. A CT scan showed a left putaminal haemorrhage (fig. 5).

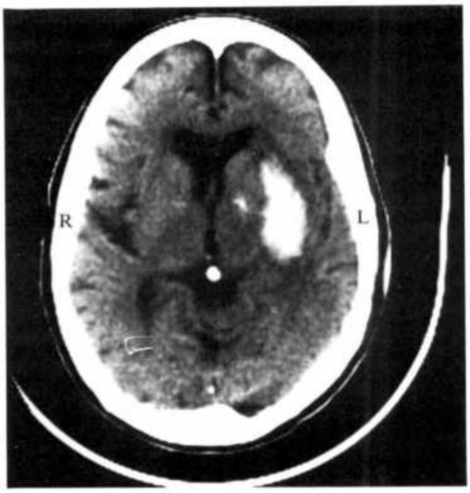


FIG. 5. CT scan showing a left putaminal haemorrhage.

Her spontaneous speech was fluent but soft, somewhat dysarthric, and mainly composed of unintelligible, low volume 'mumbling' jargon. At times, however, some utterances were punctuated by neologisms and recognizable paraphasic substitutions. Echolalia and perseverations were prominent, but serial speech was intact, and she was able to sing without prompting, using normal articulated words and proper melody. Auditory word comprehension was good, but the patient followed simple commands only intermittently, and achieved low scores in all the comprehension subtest of the WAB (Table 2) and on the Token Test (15/62). She could repeat words, phrases and even sentences composed of nonwords and/or foreign words fairly well. On the repetition subtest of the WAB, she repeated all sentences flawlessly, except the longest one. On a further repetition test composed of semantically anomalous or ungrammatical sentences (Berndt *et al.*, 1987) she corrected only 40% of syntactic errors but none of the semantic ones. She had impaired object and picture-naming (Boston Naming Test: (9/60), and she performed poorly on sentence completion (6/10), responsive speech (4/10) and word fluency tasks (animal naming: 3 words in 1 min)). Oral reading and reading comprehension were severely impaired (the score on the reading comprehension section of the WAB was 10/40).

PET scan findings. This patient showed significant decrements in metabolic activity over the entire left fronto-temporo-parietal cortex, as well as in the deep grey nuclei (lentiform, caudate and thalamus) (fig. 6) (Appendix 3). She also showed low metabolic activity in the cerebellar hemisphere contralateral to the lesion (i.e., crossed cerebellar diaschisis).

Case 19. Mixed transcortical aphasia

This patient was a 54-yr-old right-handed bilingual (Spanish-English) man, who was admitted because of the sudden onset of aphasia and right-sided weakness. On the day of admission, he had a conjugate ocular deviation to the left, a right visual field inattention, a right hemiplegia and a right sensory loss. Initially, he had no spontaneous speech, could only understand simple questions, and could point at a few common objects after a verbal command. He was unable to follow one-step commands with his left hand and to name common objects on confrontation testing, although he could repeat words and complex sentences flawlessly, but his voice was hypophonic. A WAB assessment was consistent with a MTA (Table 2). A CT scan showed a large left putaminal haemorrhage with mass effect. Three wks later, there was marked improvement in auditory comprehension and object-naming abilities. Speech was mildly dysarthric, more fluent, and with better volume, but consisted almost entirely of semantic paraphasias and neologistic distortions. Four months after the acute event, he developed a venous thrombosis in the right leg and was treated with coumadin. A new language evaluation showed that although auditory comprehension and object-naming had improved, he still had impaired comprehension of complex sequential commands and deficits in word fluency, sentence completion and responsive speech. Spontaneous speech had also improved to

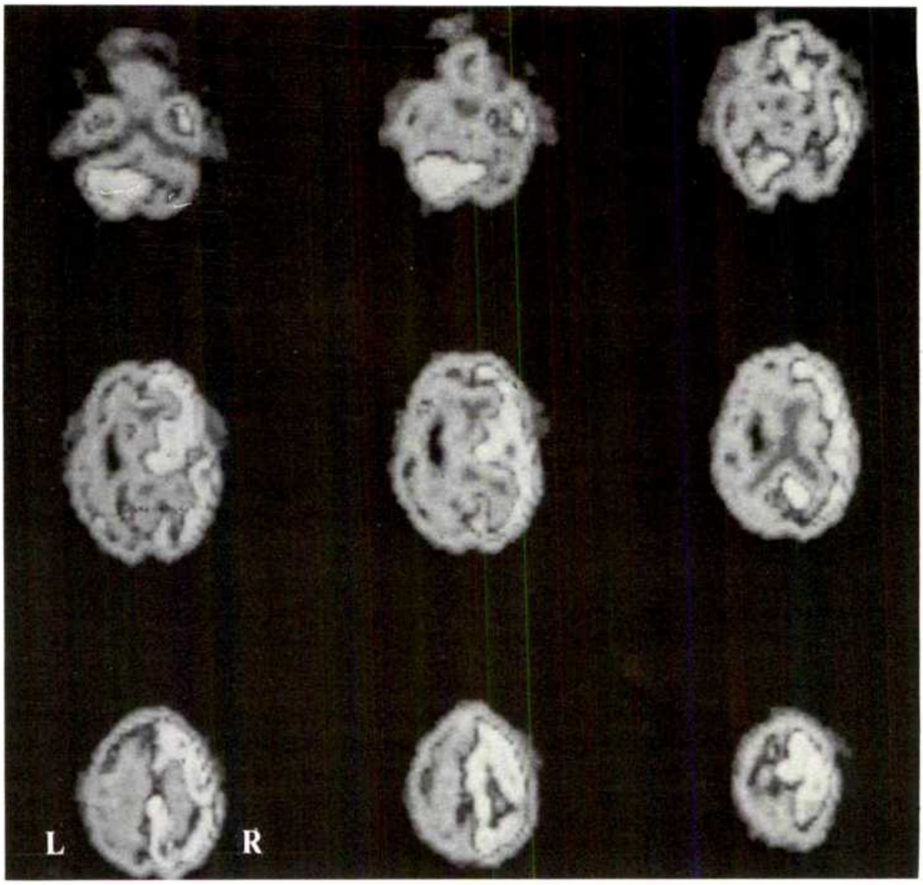


FIG. 6. 18 FDG-PET scan showing lack of metabolic activity in the entire left hemisphere (except for the occipital cortex). The right hemisphere shows normal metabolic activity.

the extent that the only prominent deficits were isolated paraphasias and word-finding difficulties. A WAB assessment was consistent with an anomic aphasia (information content 8, fluency 8, comprehension 9.2, repetition 10, naming 6.3). One year after the acute event the patient was readmitted to the hospital because of the gradual recurrence of incoherent speech and comprehension problems. On examination, he showed a residual right spastic hemiplegia, right hemisensory loss, a right hemianopia, a new left supranuclear facial weakness, gait instability and double incontinence. His language was considerably worse. Oral expression was fluent and paraphasic, and the continuous mixture of English and Spanish words made his verbal output impossible to understand. Auditory comprehension, repetition and naming had also deteriorated, and the WAB assessment was compatible with a Wernicke's aphasia (information content 5, fluency 7, comprehension 6.8, repetition 6.6, naming 2.5). A CT scan showed the old left putaminal lesion, as well as a recent haemorrhage involving the right posterior putamen and the adjacent temporal isthmus (fig. 7).

DISCUSSION

The present study showed several important findings. First, patients with TA had a similar frequency of either perisylvian or extraperisylvian pathology. Secondly, our

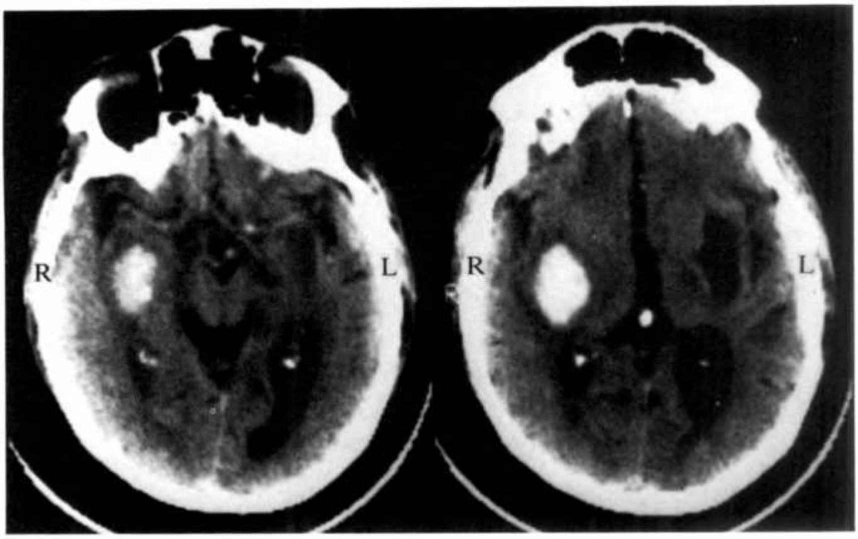


FIG. 7. CT scan showing a recent haemorrhage involving the right posterior putamen and temporal isthmus, as well as an old left putaminal lesion.

findings suggest an important role for the undamaged contralateral hemisphere in language repetition. Thirdly, further linguistic evaluation carried out in patients with transcortical sensory aphasia (TSA) showed that while all patients had a preserved nonlexical route, preservation of the lexical route was not necessary for normal repetition. Lastly, in the present study, TA was found in 17% of a consecutive series of 104 patients with acute aphasia, a frequency quite similar to a previously reported series (Kertesz, 1982), in whom language impairment was assessed using the same instrument (WAB).

The first important finding is that patients with TA showed a similar frequency of perisylvian (PS group), or extraperisylvian (EPS group) damage. PS and EPS groups were not significantly different in terms of background characteristics (i.e., age, gender, education), handedness, family history of left-handedness, and interval between disease onset and language testing. While the PS group showed a significantly more severe aphasia (i.e., significantly lower Aphasia Quotient scores on the WAB), the frequency of type of TA (TMA, TSA or MTA), and the profile of language impairments were similar for both groups. Moreover, there were no significant between-group differences in either lesion volume or measurement of cerebral asymmetries. This latter finding is in agreement with recent studies that also failed to find a significant association between cerebral dominance for language and cerebral asymmetries (Henderson *et al.*, 1984).

In summary, we could not find significant differences between PS and EPS groups that might explain the presence of preserved repetition in patients with extensive perisylvian damage.

Preserved repetition and extensive perisylvian involvement

Patients in the PS group had lesions involving large portions of the perisylvian speech area, demonstrating that the sparing of the speech area is not necessary for a preserved repetition. In 2 patients (Cases 1, 5), intracarotid amytal injections to the side contralateral to the lesion abolished language repetition. Moreover, in 1 of the patients (Case 5), the amytal injection in the carotid artery ipsilateral to the brain lesion did not worsen the patient's speech, thus excluding the participation of spared brain structures ipsilateral to the brain lesion in language repetition. Similar findings were recently reported in a right-handed patient who developed a TSA after left temporoparietal infarction (including Wernicke's area and the supramarginal gyrus) (Bando *et al.*, 1986). Although a left hemisphere injection produced no changes in language performance, an amytal injection in the right internal carotid artery abolished digit and word repetition.

Finally, it should be noted that 4 out of 5 patients with acute TSA (Cases 1, 3, 4, 5) had fluent oral expression despite extensive damage to the anterior perisylvian area (i.e., Broca's area). While similar findings have been attributed to anomalous intrahemispheric language organization (Basso *et al.*, 1985; Cases 18, 19; Alexander *et al.*, 1989), it is possible that the contralateral (spared) hemisphere may mediate some of the preserved language functions. In conclusion, although we tested the role of the right hemisphere in language repetition in a small sample and using quite heterogeneous methods, our findings are in favour of an important role of the right hemisphere in repetition among patients with TA.

Preserved repetition and 'isolation' of the speech area

Twelve patients had lesions outside the perisylvian language core (EPS group). This is consistent with the classical hypothesis that sparing of language repetition is related to the integrity of both Broca's and Wernicke's areas as well as their connecting pathways (central perisylvian area) (Geschwind *et al.*, 1968). However, the finding of preserved language repetition in 1 of these patients (Case 12), in spite of marked hypometabolism on the entire left cerebral cortex and deep cerebral structures, and the appearance of impaired repetition after a second, nondominant (right) hemisphere stroke in another patient (Case 19), make the neuroanatomical model of 'isolation' of the speech area unlikely to serve every patient with EPS lesions and TA, and suggest that the isolation of the speech area is not sufficient to preserve a normal repetition. Moreover, our findings indicate that extensive left subcortical damage (basal ganglia and/or thalamus) may induce a functional 'deactivation' of the ipsilateral cortical mantle, suggesting that spared or residual language functions, such as repetition, are carried out by the contralateral hemisphere (Cambier *et al.*, 1980). In support, recent studies by Perani *et al.* (1987, Case 3; and 1988, Case 2), using single photon emission tomography, demonstrated extensive cortical hypoperfusion ipsilateral to thalamic and/or basal ganglia in right-handed patients with MTA, suggesting that repetition was carried out by the spared hemisphere.

Lexical and nonlexical routes in patients with transcortical aphasia: role of perisylvian and extraperisylvian lesions

Recent psycholinguistic studies (McCarthy and Warrington, 1984; Coslett *et al.*, 1987) suggested that repetition may be accomplished through two functionally different routes, lexical and nonlexical. Coslett *et al.* argued that patients with TSA, who repeat using both the lexical and nonlexical routes, correct syntactic errors spontaneously but produce semantic paraphasias in spontaneous speech, whereas patients with TSA, who repeat using only the nonlexical (direct) route make both phonological and semantic paraphasias and fail to correct syntactic errors. In our study, we found that only 6 out of the 9 patients with TSA that we tested could correct syntactic errors, demonstrating that a preserved lexical route is not necessary for normal repetition. On the other hand, all 9 patients with TSA could repeat nonwords flawlessly, demonstrating a preserved nonlexical route (Coslett *et al.*, 1987). There were no significant differences between PS and EPS in the frequency of patients that corrected syntactic errors on repetition. The only significant between-group difference was found in the type of paraphasia produced during an object-naming task, since the EPS group produced significantly more semantic paraphasic errors than the PS group. This finding supports the hypothesis that, while the phonologic areas may be organized within the perisylvian speech region, the semantic areas may be organized in more peripheral brain regions (Cappa *et al.*, 1981).

Premorbid brain language lateralization in transcortical aphasia

One implication of our study concerns the premorbid brain organization of language in our patients with TA. The sparing of repetition in patients with massive damage to the perisylvian language and the potential role of the right hemisphere in sentence repetition demonstrated in 2 patients of the EPS group suggest a major contribution of both hemispheres in linguistic processes.

Since bilateral cerebral dominance for language has been reported as a relatively common finding in left-handers as well as in right-handers with a family history of left-handedness (Rasmussen and Milner, 1977; Hécaen *et al.*, 1981; Joanette *et al.*, 1983), the occurrence of TA, despite damage to the perisylvian area in 2 left-handed patients (Cases 5, 8) and in 2 right-handed patients with a family history of left-handedness (Cases 2, 6), is not surprising.

The hypothesis of bilateral hemisphere participation, however, is more difficult to apply to our right-handed patients with TA, since Rasmussen and Milner (1977) found no evidence of bilateral speech representation in a series of 140 right-handed epileptic patients in whom language lateralization was determined using sodium amytal tests. However, the amytal data obtained from epileptic patients is quite contradictory, since Mateer and Dodrill (1983) recently reported that 4 of their 6 patients with bilateral language representation were right-handed. Moreover, bihemispheric language representation has also been demonstrated using intracarotid sodium amytal tests in right-handed nonepileptic patients (Angelergues *et al.*, 1962; Kinsbourne, 1971).

All our strongly right-handed patients with TA and lesions involving large portions of the whole left perisylvian area (Cases 1, 3, 4, 7, 9) had spontaneous speech, naming, auditory comprehension and reading abilities mediated by the left hemisphere, since all these output modalities were disrupted by the lesion, and spared repetition might have been the only language function carried out by the right hemisphere. In support, impaired language repetition was the main linguistic deficit found in right-handed patients who developed a 'crossed' conduction aphasia after extensive damage to right perisylvian structures (Yarnell, 1981, Case 2; Assal, 1982; Fournet *et al.*, 1987). Therefore, our data support the hypothesis that, at least in some right-handers, the perisylvian area of the right hemisphere may mediate specific linguistic functions such as phonological processing (Schweiger *et al.*, 1987; Alexander *et al.*, 1989) and repetition. In any case, the role of the right hemisphere in linguistic functions (i.e., repetition) will need further investigation using larger samples of patients examined with similar techniques.

In conclusion, this is the first systematic study of neuroradiological correlates of language repetition in patients with TA. We found that, contrary to previous suggestions, the integrity of left hemisphere perisylvian speech regions is not necessary or sufficient for a normal repetition. Furthermore, our data also suggest that the spared contralateral hemisphere may mediate repetition abilities in patients with lesions either within or outside the perisylvian speech area. Future studies may examine the brain areas associated with preserved repetition in TA further and may explore in more detail the neurolinguistic aspects of residual repetition.

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REFERENCES

ALBERT ML, GOODGLASS H, HELMS NA, RUBENS AB, ALEXANDER MP (1981) Dysphasia without repetition disturbance: transcortical dysphasias. In: *Clinical Aspects of Dysphasia. Disorders of Human Communication 2.* Edited by G. E. Arnold, F. Winckel and B. D. Wyke. New York: Springer, pp. 93–100.

ALEXANDER MP, SCHMITT MA (1980) The aphasia syndrome of stroke in the left anterior cerebral artery territory. *Archives of Neurology, Chicago,* **37,** 97–100.

ALEXANDER MP, FISCHETTE MR, FISCHER RS (1989) Crossed aphasias can be mirror image or anomalous: case reports, review and hypothesis. *Brain,* **112,** 953–973.

ANGELERGUES R, HÉCAEN H, DJINDJIAN R, JARRIÉ-HAZAN N (1962) Un cas d'aphasie croisée: (thrombose de l'artère sylvienne droite chez une droitière). *Revue Neurologique,* **107,** 543–545.

ASSAL G (1982) Étude neuropsychologique d'une aphasie croisée avec jargonagraphie. *Revue Neurologique,* **138,** 507–515.

ASSAL G, REGLI F, THUILLARD F, STECK A, DERUAZ J-P, PERENTES E (1983) Syndrome d'isolement de la zone du langage: étude neuropsychologique et pathologique. *Revue Neurologique,* **139,** 417–424.

BANDO M, UGAWA Y, SUGISHITA M (1986) Mechanism of repetition in transcortical sensory aphasia. *Journal of Neurology, Neurosurgery and Psychiatry,* **49,** 200–202.

BASSO A, LECOURS AR, MORASCHINI S, VANIER M (1985) Anatomoclinical correlations of the aphasias as defined through computerized tomography: exceptions. *Brain and Language,* **26,** 201–229.

BASTIAN HC (1897) Some problems in connexion with aphasia and other speech defects. *Lancet,* **i,** 933–942, 1005–1017, 1131–1137, 1187–1194.

BERNDT RS, BASILI A, CARAMAZZA A (1987) Dissociation of functions in a case of transcortical sensory aphasia. *Cognitive Neuropsychology,* **4,** 79–107.

BOGOUSSLAVSKY J, REGLI F, ASSAL G (1988) Acute transcortical mixed aphasia: a carotid occlusion syndrome with pial and watershed infarcts. *Brain,* **111,** 631–641.

BOLLA-WILSON K, SPEEDIE LJ, ROBINSON RG (1985) Phonologic agraphia in a left-handed patient after a right-hemisphere lesion. *Neurology, Cleveland,* **35,** 1778–1781.

BROWN JW (1975) The problem of repetition: a study of 'conduction' aphasia and the 'isolation' syndrome. *Cortex,* **11,** 37–52.

CAMBIER J, ELGHOZI D, KHOURY M, STRUBE A (1980) Répétition écholalique et troubles sévères de la compréhension: syndrome de dé-activation de l'hémisphère gauche? *Revue Neurologique,* **136,** 689–698.

CAPPA SF, VIGNOLO LA (1979) 'Transcortical' features of aphasia following left thalamic hemorrhage. *Cortex,* **15,** 121–129.

CAPPA S, CAVALLOTTI G, VIGNOLO LA (1981) Phonemic and lexical errors in fluent aphasia: correlation with lesion site. *Neuropsychologia,* **19,** 171–177.

Coslett HB, Roeltgen DP, Gonzalez Rothi L, Heilman KM (1987) Transcortical sensory aphasia: evidence for subtypes. *Brain and Language*, **32**, 362–378.

Cummings JL, Benson DF, Hill MA, Read S (1985) Aphasia in dementia of the Alzheimer type. *Neurology, Cleveland*, **35**, 394–397.

Damasio H (1981) Cerebral localization of the aphasias. In: *Acquired Aphasia*. Edited by M. T. Sarno. New York· Academic Press, pp. 27–50.

Damasio H, Damasio A (1979) 'Paradoxic' ear extinction in dichotic listening: possible anatomic significance. *Neurology, New York*, **29**, 644–653.

Damasio AR, Van Hoesen GW (1980) Structure and function of the supplementary motor area. *Neurology, New York*, **30**, 359.

Dewan MJ, Haldipur CV, Lane E, Donnelly MP, Boucher M, Major LF (1987) Normal cerebral asymmetry in bipolar patients. *Biological Psychiatry*, **22**, 1058–1066.

Fournet F, Virat-Brassaud ME, Guard O, Dumas R, Auplat P, Marchal G (1987) Alexie-agraphie croisée chez un droitier. *Revue Neurologique*, **143**, 214–219.

Freedman M, Alexander MP, Naeser MA (1984) Anatomic basis of transcortical motor aphasia. *Neurology, Cleveland*, **34**, 409–417.

Geschwind N (1965) Disconnexion syndromes in animals and man. Parts I and II. *Brain*, **88**, 237–294, 585–644.

Geschwind N, Quadfasel FA, Segarra JM (1968) Isolation of the speech area. *Neuropsychologia*, **6**, 327–340.

Goldstein K (1948) Pictures of speech disturbances due to impairment of the non-language mental performances. In: *Language and Language Disturbances*. New York: Grune and Stratton, pp. 292–309.

Hécaen H, De Agostini M, Monzon-Montes A (1981) Cerebral organization in left-handers. *Brain and Language*, **12**, 261–284.

Henderson VW, Naeser MA, Weiner JM, Pieniadz JM, Chui HC (1984) CT criteria of hemisphere asymmetry fail to predict language laterality. *Neurology, Cleveland*, **34**, 1086–1089.

Henschen SE (1920–1922) Klinische und Anatomische Beitrage zur Pathologie des Gehirns. Volumes 5–7. Stockholm: Nordisik Bokhandeln.

Hubner O (1889) Über Aphasie. *Schmidt's Jahrbücher, Leipzig*, **224**, 220–222.

Joanette Y, Lecours AR, Lepage Y, Lamoureux M (1983) Language in right-handers with right-hemisphere lesions: a preliminary study including anatomical, genetic, and social factors. *Brain and Language*, **20**, 217–284.

Kapur N, Dunkley B (1984) Neuropsychological analysis of a case of crossed dysphasia verified at postmortem. *Brain and Language*, **23**, 134–147.

Kertesz A (1982) *The Western Aphasia Battery*. New York: Grune and Stratton.

Kertesz A, Lesk D, McCabe P (1977) Isotope localization of infarcts in aphasia. *Archives of Neurology, Chicago*, **34**, 590–601.

Kertesz A, Sheppard A, MacKenzie R (1982) Localization in transcortical sensory aphasia. *Archives of Neurology, Chicago*, **39**, 475–478.

Kinsbourne M (1971) The minor cerebral hemisphere as a source of aphasic speech. *Archives of Neurology, Chicago*, **25**, 302–306.

Kushner M, Reivich M, Alavi A, Greenberg J, Stern M, Dann R (1987) Regional cerebral glucose metabolism in aphemia: a case report. *Brain and Language*, **31**, 201–214.

Levine DN, Grek A (1984) The anatomic basis of delusions after right cerebral infarction. *Neurology, Cleveland*, **34**, 577–582.

Lichtheim L (1885) On aphasia. *Brain*, **7**, 433–484.

Luchins DJ, Meltzer HY (1983) A blind, controlled study of occipital cerebral asymmetry in schizophrenia. *Psychiatry Research*, **10**, 87–95.

McCarthy R, Warrington EK (1984) A two-route model of speech production: evidence from aphasia. *Brain*, **107**, 463–485.

Masdeu JC, Schoene WC, Funkenstein H (1978) Aphasia following infarction of the left supplementary motor area: a clinicopathologic study. *Neurology, New York*, **28**, 1220–1223.

Mateer CA, Dodrill CB (1983) Neuropsychological and linguistic correlates of atypical language lateralization: evidence from sodium amytal studies. *Human Neurobiology*, **2**, 135–142.

MATSUI T, HIRANO A (1978) *An Atlas of the Human Brain for Computerized Tomography*. Tokyo: Igaku-Shoin.

MAYBERG HS, ROBINSON RG, WONG DF, PARIKH R, BOLDUC P, STARKSTEIN SE *et al.* (1988) PET imaging of cortical S_2 serotonin receptors after stroke: lateralized changes and relationship to depression. *American Journal of Psychiatry*, **145**, 937–943.

MAYBERG HS, STARKSTEIN SE, SADZOT B, PREZIOSI T, ANDREZEJEWSKI PL, DANNALS RF *et al.* (1990) Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Annals of Neurology*, **28**, 57–64.

MEHLER MF (1988) Mixed transcortical aphasia in nonfamilial dysphasic dementia. *Cortex*, **24**, 545–554.

MOHR JP (1973) Rapid amelioration of motor aphasia. *Archives of Neurology, Chicago*, **28**, 77–82.

NAESER MA, HAYWARD RW (1978) Lesion localization in aphasia with cranial computed tomography and the Boston Diagnostic Aphasia Exam. *Neurology, New York*, **28**, 545–551.

NAESER MA, HAYWARD RW, LAUGHLIN S, ZATZ LM (1981) Quantitative CT scan studies in aphasia. Infarct size and CT numbers. *Brain and Language*, **12**, 140–164.

NIESSL VON MAYENDORF E (1911) Die aphasischen Symptome und ihre corticale Lokalisation. Leipzig: Barth.

PERANI D, VALLAR G, CAPPA S, MESSA C, FAZIO F (1987) Aphasia and neglect after subcortical stroke: a clinical/cerebral perfusion correlation study. *Brain*, **110**, 1211–1229.

PERANI D, PAPAGNO C, CAPPA S, GERUNDINI P, FAZIO F (1988) Crossed aphasia: functional studies with single photon emission computerized tomography. *Cortex*, **24**, 171–178.

PHELPS ME, HUANG SC, HOFFMAN EJ, SELIN C, SOKOLOFF L, KUHL DE (1979) Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Annals of Neurology*, **6**, 371–388.

RASMUSSEN T, MILNER B (1977) The role of early left-brain injury in determining lateralization of cerebral speech functions. *Annals of the New York Academy of Sciences*, **299**, 355–369.

REINVANG I (1987) Crossed aphasia and apraxia in an artist. *Aphasiology*, **1**, 423–434.

ROSS ED (1980) Left medial parietal lobe and receptive language functions: mixed transcortical aphasia after left anterior cerebral artery infarction. *Neurology, New York*, **30**, 144–151.

RUBENS AB (1975) Aphasia with infarction in the territory of the anterior cerebral artery. *Cortex*, **11**, 239–250.

RUBENS AB, KERTESZ A (1983) The localization of lesions in transcortical aphasias. In: *Localization in Neuropsychology*. Edited by A. Kertesz. New York: Academic Press, pp. 245–268.

SCHWEIGER A, WECHSLER AF, MAZZIOTTA JC (1987) Metabolic correlates of linguistic functions in a patient with crossed aphasia: a case study. *Aphasiology*, **1**, 415–421.

SELNES OA, RUBENS AB, RISSE GL, LEVY RS (1982) Transient aphasia with persistent apraxia: uncommon sequela of massive left-hemisphere stroke. *Archives of Neurology, Chicago*, **39**, 122–126.

SELNES OA, KNOPMAN DS, NICCUM N, RUBENS AB (1985) The critical role of Wernicke's area in sentence repetition. *Annals of Neurology*, **17**, 549–557.

SPEEDIE LJ, COSLETT HB, HEILMAN KM (1984) Repetition of affective prosody in mixed transcortical aphasia. *Archives of Neurology, Chicago*, **41**, 268–270.

STARKSTEIN SE, ROBINSON RG, BERTHIER ML, PARIKH RM, PRICE TR (1988) Differential mood changes following basal ganglia vs thalamic lesions. *Archives of Neurology, Chicago*, **45**, 725–730.

STENGEL E (1936) Zur Lehre von den transcorticalen Aphasien. *Zeitschrift für die Gesamte Neurologie und Psychiatrie*, **154**, 778–782.

STENGEL E (1947) A clinical and psychological study of echo-reactions. *Journal of Mental Science*, **93**, 598–612.

TROJANO L, FRAGASSI NA, POSTIGLIONE A, GROSSI D (1988) Mixed transcortical aphasia. On relative sparing of phonological short-term store in a case. *Neuropsychologia*, **26**, 633–638.

VIX E (1910) Anatomischer Befund zu dem in Band 37 dieses Archivs veröffentlichten Fall von transkortikaler sensorischer Aphasie. *Archiv für Psychiatrie und Nervenkrankheiten*, **47**, 200–212.

WERNICKE C (1885–1886) Einige Neuere Arbeiten uber Aphasie. *Fortschritte der Medizin*, **3**, 463. Translated in: *Wernicke's Works on Aphasia*. Edited by G. H. Eggert. Paris: Mouton, pp. 173–205.

WHITAKER H (1976) A case of isolation of language function. In: *Studies in Neurolinguistics*, Volume 1. Edited by H. Whitaker and H. A. Whitaker. New York: Academic Press, pp. 1–58.

YARNELL PR (1981) Crossed dextral aphasia: a clinical radiological correlation. *Brain and Language*, **12**, 128–139.

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APPENDIX 1

Amytal test

The angiographic procedure was performed via transfemoral catheterization of the internal carotid artery. A control angiogram was carried out to exclude occlusion of the internal carotid artery or its major branches, and the presence of abnormal vessel patterns (e.g., cross-filling of the contralateral anterior cerebral artery). Patients were instructed to raise both arms, and a dose of 125 mg sodium amobarbital in a 10% saline solution was hand-injected over 4 s The drug effect was confirmed by EEG monitoring and the presence of contralateral hemiplegia, hemianopia, and ipsilateral conjugated eye deviation. Language testing was started as soon as patients became alert and cooperative, and it continued during the period of persistence of the contralateral hemiplegia and ipsilateral slowing on EEG. Language assessment included measures of (1) automatic speech (counting forwards, recitation of the days), (2) repetition (concrete words and 4-word sentences), (3) confrontation naming (10 common objects), (4) auditory comprehension (pointing to geometric designs in response to increasingly complex commands), and (5) reading of simple words.

APPENDIX 2

^{18}FDG PET scan study

The ^{18}FDG PET scan procedure was performed as follows (Mayberg *et al.*, 1988). A CT scan was obtained using an imaging plane parallel to the glabellar-inion line, which passed symmetrically through the area of lesion documented by the CT evaluation An alignment was drawn on a thermoplastic, individually fitted mask which was subsequently used to establish the 12 imaging planes in the ^{18}FDG PET study. ^{18}FDG was injected in a quiet room, with the patient awake but with eyes closed. The scanning procedure started 45 min after the radiotrace injection. Twelve contiguous slices incorporating the full rostrocaudal extent of the brain were obtained. Images were acquired in the high resolution mode (slice thickness 1.6 cm, in plane resolution 0.8 cm). Data were corrected for attenuation and radioactive decay. Absolute metabolic rates for glucose (CMRglu) were calculated using previously described methods (Phelps *et al.*, 1979). The whole brain metabolic rate was calculated by averaging the CMRglu of cortical and subcortical regions from multiple slices (approximately 70 regions of equal size in each hemisphere). Regions of interest (ROIs) were drawn in symmetric left and right cortical areas. Finally, results were compared with findings in a group of 4 normal controls (Mayberg *et al.*, 1990)

APPENDIX 3

Regional cerebral glucose metabolism (AI)

Region	*Case 12*	*Normal controls*
Inferior frontal cortex	23.07*	1.0 (0.9)
Superior frontal cortex	39.35*	−1.9 (1.3)
Mesial frontal cortex	18.27*	5.0 (2.0)
Insular cortex	31.91*	1.0 (1.7)
Temporal cortex	28.26*	2.2 (0.7)
Parietal cortex	39.87*	0.2 (3.7)
Caudate nucleus	40.91*	−1.6 (1.7)
Lentiform nucleus	53.71*	0.71 (3.5)
Thalamus	56.26*	0.18 (2.3)
Cerebellum	−49.63	−2.05 (4.5)

This table compares asymmetries of CMRglu between homologous regions in the 2 cerebral hemispheres. In order to compare the CMRglu between homologous brain regions in the left hemisphere, an Asymmetry Index (AI) was calculated (Kushner *et al*, 1987) Mean values in the AI for the normal controls are shown in the last column along with the SD in parentheses. A positive AI value indicates a relatively lower value for CMRglu on the left. * Lies beyond the 95% cut-off anticipated for the normal distribution

Brain (1991), **114**, 1429–1440

D1/D2 DOPAMINE RECEPTOR STIMULATION BY L-DOPA

A [^{14}C]-2-DEOXYGLUCOSE AUTORADIOGRAPHIC STUDY

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SUMMARY

In rats with unilateral 6-hydroxydopamine substantia nigra lesions, the effects of selective D1 and D2 dopamine receptor antagonists on L-DOPA-induced rotation and regional cerebral glucose utilization (RCGU) changes were examined. Contralateral rotation induced by L-DOPA (25 mg/kg) was effectively blocked by D1 (SCH 23390, 1.0 mg/kg) and D2 (eticlopride, 2.0 mg/kg) antagonists, in combination, but not by either antagonist alone. This suggests that in the dopamine-depleted rat, L-DOPA administration results in the stimulation of both D1 and D2 receptor systems, each capable of independently eliciting a full motor response. L-DOPA altered RCGU in the following brain regions ipsilateral to the lesion: entopeduncular nucleus (EP, +105%), substantia nigra pars reticulata (SNr, +121%), subthalamic nucleus (STN, +32%), deep layers of the superior colliculus (DLSC, +35%), and lateral habenula nucleus (LHN, −52%). The effects in the EP and SNr were blocked completely by D1 antagonist pretreatment but only partially attenuated by D2 antagonist pretreatment, indicating the critical dependence of these changes on D1 stimulation. In contrast, combined D1 and D2 antagonist pretreatment, but neither drug alone, blocked the L-DOPA-induced increases in the STN and DLSC. The effects of L-DOPA in the LHN were attenuated by either SCH 23390 or eticlopride, and blocked completely by the antagonist combination. These results provide evidence that dopamine formed following the decarboxylation of L-DOPA stimulates both D1 and D2 receptors in vivo and that stimulation of each receptor contributes uniquely to its physiological effects. Neural mechanisms of action of L-DOPA are discussed in the context of these findings.

INTRODUCTION

More than 20 years after its introduction into clinical medicine (Cotzias *et al.*, 1969), L-3,4 dihydroxyphenylalanine (L-DOPA) remains the mainstay of the drug treatment of Parkinson's disease. Yet quality of life during long-term L-DOPA therapy is compromised by drug-induced dyskinesias and other complex treatment-related fluctuations. The sustained clinical improvement obtained with continuous dopaminergic stimulation in a select population of parkinsonian patients (Frankel *et al.*, 1990) suggests that the neural systems which transduce and mediate the effects of L-DOPA remain intact even after 15 or more years of disease duration. This raises the important question of whether the therapeutic and adverse effects of L-DOPA are separable, as suggested by the studies of Mouradian *et al.* (1988), and exposes several gaps in our understanding

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of its basic mechanism of action. Key questions which remain unanswered include: (1) What are the relative contributions of D1 and D2 dopamine receptor stimulation to the clinical effects of L-DOPA? (2) Does L-DOPA have actions outside of the caudate-putamen and can different regional sites of action be correlated with distinct behavioural effects?

In rats with unilateral 6-hydroxydopamine (6-OHDA) lesions of the substantia nigra, a classical animal model of Parkinson's disease (Ungerstedt *et al.*, 1973), we have used the 2-deoxyglucose (2-DG) autoradiographic method of measuring regional cerebral glucose utilization (RCGU) to identify brain regions physiologically altered by dopaminergic drugs. Systemically administered L-DOPA markedly increased RCGU in the entopeduncular nucleus (EP; homologue of the primate globus pallidus, internal segment (GPi)) and substantia nigra pars reticulata (SNr) ipsilateral to the nigral lesion and resulted in moderate RCGU increases in the ipsilateral subthalamic nucleus (STN) and deeper layers of the superior colliculus (DLSC) (Trugman and Wooten, 1986). The marked RCGU increases in the EP and SNr were reproduced by the selective D1 agonist SKF 38393 but not by the selective D2 agonist quinpirole (Trugman and Wooten, 1987), suggesting, but not proving, that some of the metabolic effects of L-DOPA are mediated by D1 stimulation. In the present study we have examined the effects of selective D1 and D2 antagonists on L-DOPA-induced contralateral rotation and RCGU changes to determine the relative contributions of D1 and D2 receptor stimulation to the effects of L-DOPA.

METHODS

Animal preparation

All experiments were performed on male Sprague-Dawley rats weighing 225–275 g at the time of lesion. Following pretreatment with desipramine hydrochloride, 25 mg/kg, i.p. (Sigma Chemical Co., St Louis, MO), unilateral, left-sided, 6-OHDA lesions of the substantia nigra pars compacta were performed as previously described (Wooten and Collins, 1981); 6-hydroxydopamine hydrobromide (9.6 μg/2.4 μl of 0.1% ascorbic acid in saline) was injected over 5 min at the following stereotactic coordinates: bregma −5.0 mm posterior, 1.6 mm lateral, −8.0 mm ventral (Paxinos and Watson, 1982). Rats were tested 10 days later with apomorphine hydrochloride (Sigma), 0.5 mg/kg, i.p., to determine lesion efficacy. Only rats that turned a minimum of 5 rotations/min at the peak action of apomorphine were used in subsequent rotational and 2-DG studies, performed 4–6 wks after lesioning.

Drugs

Drugs were prepared as follows: L-DOPA methyl ester (Sigma), SCH-23390 (R(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine HCl) and (−)-eticlopride hydrochloride (Research Biochemicals Inc., Natick, MA) were dissolved in water. Carbidopa (Merck, Sharp and Dohme Research Laboratories, West Point, PA) was prepared as an aqueous suspension. Drugs were injected in a volume of 1.0 ml/kg body weight. Drug doses are expressed in terms of the weights of their salts.

Experimental design and data analysis

Rotational experiments. The effects of D1, D2, and combined D1 and D2 antagonist pretreatment on L-DOPA-induced rotation were assessed in 8 lesioned rats. Each rat received each drug treatment once. A replicated 4×4 Latin square design was used to randomize the sequence of drug treatments. Testing sessions were separated by 5–7 days.

Rats were placed into 32 cm diameter cylindrical containers and allowed to acclimatize to this environment for 30 min. SCH 23390 (1.0 mg/kg), eticlopride (2.0 mg/kg), and carbidopa (25 mg/kg) were administered i.p. 30 min before the administration of L-DOPA (25 mg/kg i.p.). The doses of SCH 23390 and eticlopride were chosen on the basis of their ability to occupy >95% of striatal D1 and D2 receptors, respectively, following systemic administration (Hall *et al.*, 1985; Köhler *et al.*, 1985; Leslie and Bennett, 1987); 360° contralateral rotations were counted for 2 min every 10 min for the duration of the experiment (3 h and 50 min). Analysis of variance followed by the Duncan multiple range test was used to analyse the data.

2-DG experiments. Rats with unilateral substantia nigra lesions were segregated into 5 treatment groups: (1) distilled water control; (2) L-DOPA (25 mg/kg); (3) SCH 23390/L-DOPA (1.0/25 mg/kg); (4) eticlopride/L-DOPA (2.0/25 mg/kg); (5) SCH 23390/eticlopride/L-DOPA (1.0/2.0/25 mg/kg). Antagonists were given intravenously 1 h before i.v. L-DOPA administration. Carbidopa (25 mg/kg) was given i.p. 30 min before L-DOPA. On the day of the experiment, after the rats had been fasted overnight, central venous catheters were inserted under 1% halothane anaesthesia, followed by a 3 h recovery period. Rats were injected i.v. with [^{14}C]-2-DG (8 μCi/100 g body weight in 0.3–0.4 ml saline; 55 mCi/mM; American Radiochemical, St Louis, MO) 2–3 min after L-DOPA administration. Unrestrained rats were studied in 23×35 cm cages. The rats were killed with a 50 mg/ml intravenous bolus of sodium pentobarbital 45 min after the [^{14}C]-2-DG injection. The brains were rapidly removed and frozen in liquid freon. Duplicate 20 μm coronal sections were taken every 100 μm, thaw-mounted on coverslips, dried on a 40° C warming tray, and exposed on Kodak SB-5 x-ray film for 5 days. Film autoradiographs were analysed with a Leitz variable aperture microdensitometer.

Data for glucose utilization were expressed as a ratio of grey matter to corpus callosum optical densities (relative 2-DG uptake; Mitchell and Crossman, 1984). Relative 2-DG uptake is linearly related to calculated rates of glucose utilization expressed as μmol/100 g/min and accurately measures changes induced by pharmacological and physiological stimuli (Sharp *et al.*, 1983; Geary and Wooten, 1987). The data represent the mean ± SEM of a minimum of 4–6 optical density measurements per brain region per animal; n = 5–10 rats per group. Data were analysed using the Duncan multiple range test. Left/right comparisons were made using Student's paired t test (Snedecor and Cochran, 1967). Statistical significance was taken as $P < 0.05$.

RESULTS

Rotational experiments

The effects of D1, D2, and combined D1 plus D2 antagonist pretreatment on L-DOPA-induced contralateral rotation are illustrated in fig. 1. It is clear that only the D1 plus D2 antagonist combination (SCH 23390+eticlopride) effectively blocked L-DOPA-

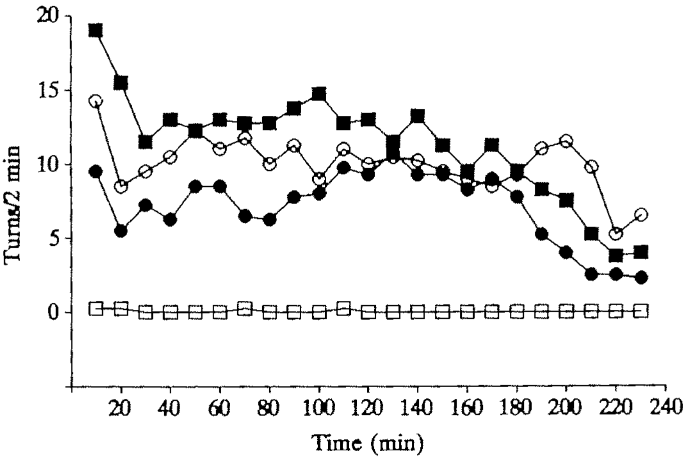


FIG. 1. Effect of SCH 23390 (1.0 mg/kg) (closed circles), eticlopride (2.0 mg/kg) (closed squares), and both drugs in combination (open squares) on contralateral rotation induced by L-DOPA (25 mg/kg) (open circles). L-DOPA was given i.p at time zero. n = 8 rats per group.

induced rotation and this was confirmed by the Duncan multiple range test ($P < 0.01$). The means ± SEM of the cumulative turns per rat observed over the 23 2 min observation periods were as follows: L-DOPA, 230±41; eticlopride/L-DOPA, 259±72; SCH 23390/L-DOPA, 164±27; eticlopride/SCH 23390/L-DOPA, 1±0.5. Analysis of variance of the 3 other treatment groups (L-DOPA, eticlopride/L-DOPA, and SCH 23390/L-DOPA) failed to demonstrate a difference in cumulative turns over the course of the experiment. In addition, no statistically significant differences were found when the data for the first 45 min, first 2 h, and second 2 h were analysed separately.

Regional cerebral glucose utilization

Data are presented in the Table. Several asymmetries were noted in rats with unilateral 6-OHDA nigral lesions, in general agreement with previous studies (Kozlowski and Marshall, 1980; Wooten and Collins, 1981; Trugman and Wooten, 1986). Expressed as the percentage difference in optical density ratios between the region ipsilateral to the lesion and the contralateral side, the control group of lesioned rats demonstrated increased RCGU in the globus pallidus (GP, +14%) and lateral habenular nucleus (LHN, +21%) and decreased RCGU in the striatum (−6%), STN (−7%) and DLSC (−6%; all changes significant at $P < 0.05$).

TABLE. RELATIVE 2-DG UPTAKE IN RATS WITH LEFT-SIDED UNILATERAL 6-OHDA SUBSTANTIA NIGRA LESIONS

Brain region	*Side*	*Control*	*L-DOPA (25 mg/kg)*	*SCH/DOPA (1.0/25 mg/kg)*	*Etic/DOPA (2.0/25 mg/kg)*	*SCH/Etic/DOPA (1.0/2.0/25 mg/kg)*
Striatum	L	3.11 ± 0.02	3.44 ± 0.09	3.34 ± 0.15	3.35 ± 0.14	2.94 ± 0.10
	R	3.32 ± 0.05	3.43 ± 0.08	3.46 ± 0.17	3.59 ± 0.13	3.18 ± 0.13
Globus pallidus	L	2.36 ± 0.06	2.27 ± 0.06	2.38 ± 0.13	2.63 ± 0.10	2.26 ± 0.17
	R	2.06 ± 0.04	2.27 ± 0.07	2.18 ± 0.08	2.80 ± 0.19**	2.05 ± 0.09
Entopeduncular nucleus	L	1.79 ± 0.05	3.69 ± 0.18**	2.07 ± 0.13	2.94 ± 0.17**	1.67 ± 0.06
	R	1.79 ± 0.04	2.00 ± 0.06*	1.81 ± 0.04	2.11 ± 0.09*	1.74 ± 0.05
Lateral habenula	L	4.35 ± 0.19	2.07 ± 0.05**	3.38 ± 0.09**	2.71 ± 0.14**	4.81 ± 0.27**
	R	3.59 ± 0.10	5.31 ± 0.24*	5.55 ± 0.53*	5.43 ± 0.23*	5.29 ± 0.30*
Subthalamic nucleus	L	3.02 ± 0.07	3.99 ± 0.13*	3.81 ± 0.26*	3.87 ± 0.16*	2.54 ± 0.09**
	R	3.26 ± 0.09	3.71 ± 0.12*	3.55 ± 0.16	3.24 ± 0.12	2.59 ± 0.09**
Substantia nigra pars reticulata	L	2.01 ± 0.04	4.45 ± 0.35**	2.35 ± 0.12	3.35 ± 0.15**	1.87 ± 0.05
	R	2.04 ± 0.04	2.41 ± 0.09*	2.16 ± 0.11	2.50 ± 0.10*	2.02 ± 0.07
Superior colliculus, deep layers	L	2.84 ± 0.09	3.85 ± 0.13*	3.59 ± 0.25*	3.40 ± 0.14*	2.47 ± 0.07
	R	3.01 ± 0.05	3.36 ± 0.10*	3.15 ± 0.14	3.06 ± 0.11	2.49 ± 0.08*

Data represent the mean ± SEM of the optical density ratio of grey matter to corpus callosum. Controls are lesioned rats treated with water, n = 5 − 10 rats per group. * Significant difference from the control; ** Significant difference from all other groups ($P < 0.05$).

L-DOPA (25 mg/kg) altered RCGU in the following brain regions ipsilateral to the 6-OHDA lesion: EP (+105%), SNr (+121%), STN (+32%), DLSC (+35%) and LHN (−52%). These results are similar to those previously reported (Trugman and Wooten, 1986). With the exception of the STN, where increases were observed bilaterally, RCGU changes induced by L-DOPA were asymmetric (left vs right, $P < 0.01$).

In both the EP and SNr, pretreatment with a selective D1 antagonist (SCH 23390, 1.0 mg/kg) blocked the RCGU increases elicited by L-DOPA, returning values to levels statistically indistinguishable from controls. In contrast, pretreatment with a selective D2 antagonist (eticlopride 2.0 mg/kg) attenuated (by approximately 40−50%), but did not block completely, the L-DOPA-induced RCGU increases in these nuclei. Combined antagonist pretreatment completely abolished the L-DOPA-induced RCGU increases in the EP and SNr (*see* figs 2, 3).

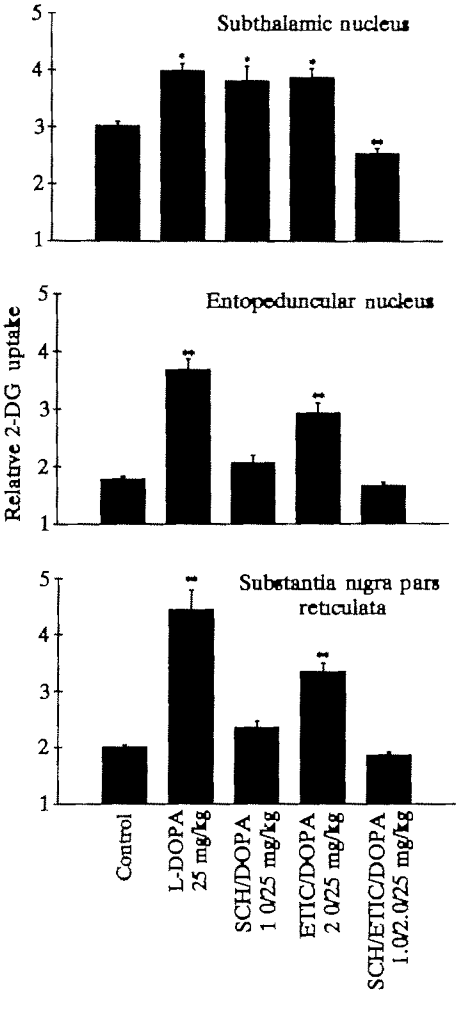
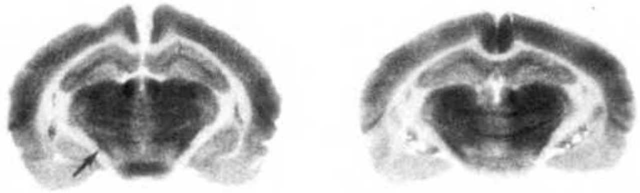


FIG. 2. Glucose utilization in 3 basal ganglia nuclei *ipsilateral* to the 6-OHDA substantia nigra lesion. * Different from the control. ** Different from all other groups ($P < 0.05$).

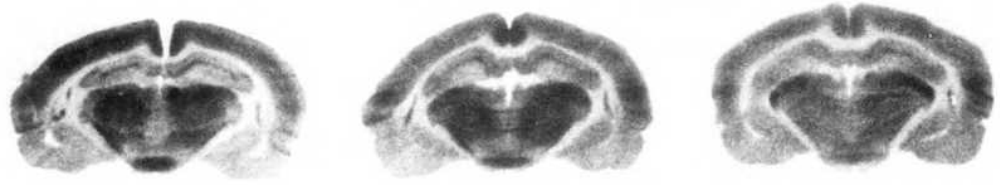
Combined D1 and D2 antagonist pretreatment, but neither drug alone, blocked the L-DOPA-induced RCGU increases in the STN and DLSC ipsilateral to the lesion. Pretreatment with either SCH 23390 or eticlopride attenuated the ability of L-DOPA to lower RCGU in the ipsilateral LHN. Combined antagonist pretreatment completely blocked this response.

Glucose utilization in the striatum and globus pallidus was unaltered by L-DOPA. Administration of eticlopride followed by L-DOPA, however, markedly increased RCGU in the globus pallidus of the nondenervated hemisphere.



Control

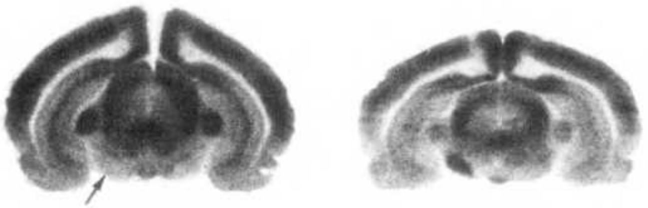
L-DOPA
25 mg/kg



SCH 23390/L-DOPA
1.0/25 mg/kg

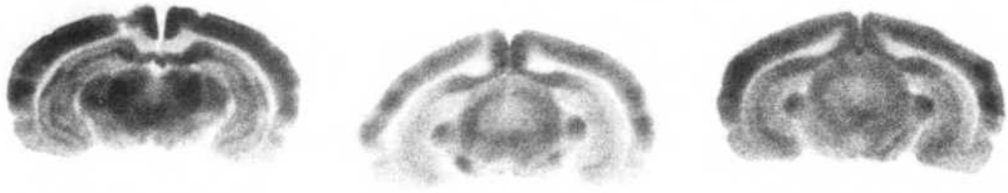
Eticlopride/L-DOPA
2.0/25 mg/kg

SCH/Etic/L-DOPA
1.0/2.0/25 mg/kg



Control

L-DOPA
25 mg/kg



SCH 23390/L-DOPA
1.0/25 mg/kg

Eticlopride/L-DOPA
2.0/25 mg/kg

SCH/Etic/L-DOPA
1.0/2.0/25 mg/kg

FIG. 3. [^{14}C]-2-DG autoradiographs depicting RCGU patterns in rats with left-sided 6-OHDA substantia nigra lesions. Arrows point to the subthalamic nucleus (STN, *top panel*) and substantia nigra pars reticulata (SNr, *bottom panel*) ipsilateral to the lesion. The RCGU increases induced by L-DOPA in the STN and SNr were differentially blocked by selective D1 (SCH 23390, 1.0 mg/kg) and D2 (eticlopride, 2.0 mg/kg) antagonist pretreatment.

DISCUSSION

The central new finding of this study is that the effects of L-DOPA on basal ganglia glucose utilization are differentially altered by D1 and D2 receptor blockade with pharmacologically selective antagonists. It is known that turning elicited by L-DOPA in lesioned rats is dependent on the enzymatic conversion of L-DOPA to dopamine in the striatum (Melamed *et al.*, 1984). The present results extend this observation by providing evidence that dopamine formed following the decarboxylation of L-DOPA stimulates both D1 and D2 receptors in vivo and that stimulation of each receptor contributes uniquely to its physiological effects.

The behavioural data presented here suggests that neither the D1 nor the D2 antagonist alone effectively blocks contralateral rotation produced by L-DOPA. In contrast, the D1 plus D2 antagonist combination completely blocked locomotor behaviour. These results agree entirely with those of Sonsalla *et al.* (1988) in which no attenuation of L-DOPA-induced rotation was obtained with either haloperidol (0.25 or 1.0 mg/kg, a selective D2 antagonist) or SCH 23390 (0.25 mg/kg) alone but total blockade was achieved by haloperidol (0.25 mg/kg) and SCH 23390 (0.25 mg/kg) in combination. These data suggest that in the dopamine-depleted rat, stimulation of either D1 or D2 receptor system is capable of independently eliciting a full motor response, a concept with much experimental support (*see* Waddington and O'Boyle, 1989, for a review). This apparent functional independence of D1 and D2 systems contrasts markedly with data from normal experimental animals in which D1 and D2 systems are highly dependent and interactive, and full dopaminergic effects result only from concurrent D1 and D2 receptor stimulation (Walters *et al.*, 1987). A clarification of the mechanisms responsible for this change in D1/D2 interaction in states of dopamine deficiency, along with an understanding of species differences, should prove critical to understanding the response to dopaminergic drugs in Parkinson's disease.

Functional anatomy of dopamine replacement therapy

The autoradiographic method of measuring glucose utilization is based on the differential uptake of tracer doses of [^{14}C]-2-DG, a structural analogue of glucose, into various tissue elements within the brain. Since glucose is the primary substrate for cerebral oxidative metabolism, the accumulation of [^{14}C]-2-DG over the 45 min experimental period represents a complex time-integrated index of physiological activity (Sokoloff, 1977). In stimulated neural tissue, it is nerve endings and dendrites which show the greatest increase in glucose utilization because it is there that surface to volume ratios are highest and energy for transmembrane ion pumping is expended at the highest rate per unit volume of tissue (Mata *et al.*, 1980). Thus in many instances, RCGU is thought to reflect predominantly activity in nerve terminals as opposed to cell bodies (Kadekaro *et al.*, 1985). The concept of RCGU as an 'index of synaptic activity' provides a useful guideline to interpretation but correlations with electrophysiology must be made in each case to assess a given RCGU change accurately. In the discussion which follows we will attempt to synthesize the actions of L-DOPA by correlating RCGU data with neurochemical anatomy and electrophysiology.

Since the GPi and the SNr are the principal output nuclei of the basal ganglia, it is likely that the major clinical effects of L-DOPA are mediated via altered activity of these nuclei. L-DOPA can alter the output of these nuclei directly by actions on striato-SNr and striato-GPi neurons and indirectly via the external segment of the GP (GPe; i.e., by modulating the activity of the GPe-STN-GPi/SNr circuit). The marked RCGU increases in the EP and SNr, shown here to be dependent on D1 stimulation, support a direct influence of L-DOPA on striato-EP and striato-SNr neurons. Correlative data suggest that these increases represent enhanced metabolic activity primarily in axon terminals of the inhibitory striatal projection neurons (Trugman and Wooten, 1986, 1987). In 6-OHDA lesioned rats, systemically administered apomorphine (a mixed D1/D2 agonist) profoundly inhibits the firing of SNr ouptut neurons (Waszczak *et al.*, 1984). This effect is reproduced by coadministration of selective D1 and D2 agonists and is effectively reversed by D1 antagonists (Weick and Walters, 1987). The ability of D1 agonists to facilitate GABA release in the dorsal striatum (Girault *et al.*, 1986) and to increase firing rates of striatonigral neurons (Weick and Walters, 1988) is consistent with a D1 receptor-mediated stimulation of striatal GABAergic neurons. In monkeys with hemiparkinsonism, L-DOPA increases RCGU in the GPi and SNr (Porrino *et al.*, 1987*a*, *b*) while apomorphine silences the enhanced firing of GPi neurons (Filion, 1979; Filion *et al.*, 1986). The RCGU decrement in the ipsilateral LHN elicited by L-DOPA in both rats and monkeys (Porrino *et al.*, 1987*b*) probably reflects this inhibition of GPi neuronal activity. To synthesize these data, increased RCGU in the EP and SNr appears to correlate with decreased firing rates of the output neurons of these nuclei. The RCGU and electrophysiological data suggest that while both D1 and D2 stimulation contribute to these effects of L-DOPA, D1 stimulation is critical.

Dopamine synthesized in dendrites of pars compacta neurons has modulatory actions in the SNr (Cheramy *et al.*, 1981). The role of dopamine in the GPi, a nucleus structurally and functionally analogous to the SNr, has been less well understood. Recently, a dense dopaminergic axonal innervation of the GPi, originating in the midbrain, has been observed in the squirrel monkey, suggesting a functional role for dopamine in this nucleus (Parent and Smith, 1987). In rat, cat, monkey, and human brain, D1 receptors are selectively enriched both in the GPi and SNr (Richfield *et al.*, 1987; Beckstead *et al.*, 1988; Cortés *et al.*, 1989). Studies using excitotoxic amino acid lesions of the striatum in rat have suggested that D1 receptors in the EP and SNr are located on the terminals of afferents from the striatum (Altar and Hauser, 1987). Moreover, nigral injections of the retrogradely transported cytotoxin, volkensin, have suggested that approximately 95% of striatal D1 receptors are located on projection neurons to the nigra (Harrison *et al.*, 1990). Thus the GPi and SNr receive dopaminergic innervation and exhibit high densities of D1 receptors which appear to be expressed on the terminals of striatal projection neurons. Studies employing local injections into the SNr support a role for nigral D1 stimulation in the motor behaviour elicited by L-DOPA and dopamine agonists (Kozlowski *et al.*, 1980; Robertson and Robertson, 1989). These studies support the thesis that dopamine formed from L-DOPA activates a population of striato-EP and striato-SNr neurons directly by stimulating D1 receptors on these cells (perhaps at both cell body and nerve terminal sites) and that RCGU functionally maps this activation.

The indirect circuit (striatum-GPe-STN-GPi/SNr) represents the other major anatomical route by which L-DOPA can alter activity in the basal ganglia output nuclei. Although pallidal RCGU does not change following L-DOPA, it is likely that firing rates of pallidal neurons do change. Dopamine agonists increase GPe firing rates in both dopamine-denervated and intact rats, effects considered to be mediated, at least in part, via inhibition of striatopallidal GABAergic neurons (Carlson *et al.*, 1990). Since the major afferent to the STN is a GABAergic projection from the GPe (Carpenter *et al.*, 1981), rate increases in the GPe should be reflected as increased RCGU in the STN, which is what is observed following L-DOPA administration. Although the electrophysiology has not been studied, a concomitant decrease in tonic firing rates of STN neurons would be predicted. Injection of the GABA antagonist, bicuculline, into the GPe results in contralateral dyskinesia and increased RCGU in the ipsilateral STN (Mitchell *et al.*, 1989). Crossman and colleagues postulate that this injection blocks striatopallidal GABAergic transmission resulting in disinhibition of the GPe-STN GABAergic projection. This would result in inhibition of STN neurons, functionally equivalent to an ablative lesion of the nucleus. If this postulated mechanism is correct, the RCGU data suggest that L-DOPA may induce dyskinesia by a similar neural mechanism (i.e., stimulation of the GPe-STN inhibitory projection; Crossman, 1990). The fact that neither D1 nor D2 antagonist alone blocked the RCGU increase in the STN, but the antagonist combination did, suggests that both D1 and D2 stimulation contribute to this effect, and perhaps to the induction of dyskinesia. Since the STN provides excitatory drive to the EP/SNr (Kitai and Kita, 1987), functional inhibition of its output could contribute to the decreased firing rates observed in the output nuclei following dopamine agonist treatment. It is not likely, however, that this mechanism would contribute to the RCGU increases in these nuclei, since it represents a decrease in the level of synaptic input.

L-DOPA increased RCGU in the DLSC, an effect which was blocked only by the D1 and D2 antagonist combination. It is known that, in this rat model, L-DOPA (like mixed dopamine agonists) inhibits the firing of SNr output neurons (B. G. Weick and J. R. Walters, personal communication). Tectal neurons are under tonic inhibition by the output neurons of the SNr and when SNr cell firing pauses, there is a time-locked bursting of tecto-spinal-diencephalic neurons (Chevalier *et al.*, 1985). It is therefore likely that the increased RCGU in the DLSC reflects primarily this bursting of tectal neurons, rather than altered synaptic input. In primates, the output of the SNr to the superior colliculus is important in the control of saccadic eye movements (Wurtz and Hikosaka, 1986) and single doses of L-DOPA improve deficits in saccadic accuracy in parkinsonian patients (Rascol *et al.*, 1989). The metabolic data presented here demonstrate that L-DOPA, acting via both D1 and D2 receptor stimulation, alters functional activity in the nigrocollicular pathway and suggest that SNr output to brainstem premotor centres may mediate some of its therapeutic effects in Parkinson's disease.

To summarize, in states of dopamine deficiency, systemically administered dopamine

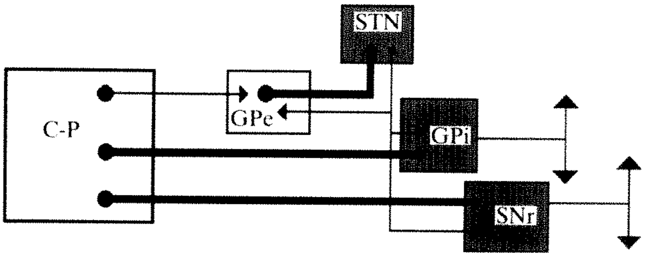


FIG. 4. Schematic diagram illustrating the major effects of L-DOPA within the basal ganglia. Bold lines signify enhancement and thin lines reduction in the net activity of each neural pathway. Shaded areas indicate regions of increased [^{14}C]-2-DG uptake. Activation of the pathways from the caudate-putamen (C-P) to GPi and SNr is critically dependent on D1 receptor stimulation (i.e., blocked by the D1 antagonist alone), whereas activation of the GPe-STN pathway is blocked only by combined D1 and D2 receptor antagonism. The projections of the GPi and SNr to thalamic and brainstem nuclei are schematically represented by the up and down arrows.

agonists inhibit cell firing in the GPi/SNr. It is proposed that dopamine can produce this net inhibition by a direct influence on striato-GPi and striato-SNr neurons as well as indirectly via the striato-GPe-STN-GPi/SNr circuit. The RCGU data support both a direct stimulatory action of dopamine on D1 receptor-bearing striatal GABAergic neurons projecting to the GPi/SNr as well as a net stimulatory action on the GPe output to the STN (fig. 4). The metabolic effects in the EP/SNr appear to be critically dependent on D1 stimulation whereas the effects in the STN are only blocked by simultaneous D1/D2 receptor antagonism.

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REFERENCES

ALTAR CA, HAUSER K (1987) Topography of substantia nigra innervation by D_1 receptor-containing striatal neurons. *Brain Research, Amsterdam*, **410**, 1–11.

BECKSTEAD RM, WOOTEN GF, TRUGMAN JM (1988) Distribution of D1 and D2 dopamine receptors in the basal ganglia of the cat determined by quantitative autoradiography. *Journal of Comparative Neurology*, **268**, 131–145.

CARLSON JH, BERGSTROM DA, DEMO SD, WALTERS JR (1990) Nigrostriatal lesion alters neurophysiological responses to selective and nonselective D-1 and D-2 dopamine agonists in rat globus pallidus. *Synapse*, **5**, 83–93.

CARPENTER MB, CARLETON SC, KELLER JT, CONTE P (1981) Connections of the subthalamic nucleus in the monkey. *Brain Research, Amsterdam*, **224**, 1–29.

CHERAMY A, LEVIEL V, GLOWINSKI J (1981) Dendritic release of dopamine in the substantia nigra. *Nature, London*, **289**, 537–542.

CHEVALIER G, VACHER S, DENIAU JM, DESBAN M (1985) Disinhibition as a basic process in the expression of striatal functions. I. The striato-nigral influence on tecto-spinal/tecto-diencephalic neurons. *Brain Research, Amsterdam*, **334**, 215–226.

CORTÉS R, GUEYE B, PAZOS A, PROBST A, PALACIOS JM (1989) Dopamine receptors in human brain: autoradiographic distribution of D_1 sites. *Neuroscience*, **28**, 263–273.

COTZIAS GC, PAPAVASILIOU PS, GELLENE R (1969) Modifications of parkinsonism—chronic treatment with L-DOPA. *New England Journal of Medicine*, **280**, 337–345.

CROSSMAN AR (1990) A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. *Movement Disorders*, **5**, 100–108.

FILION M (1979) Effects of interruption of the nigrostriatal pathway and of dopaminergic agents on the spontaneous activity of globus pallidus neurons in the awake monkey. *Brain Research, Amsterdam*, **178**, 425–441.

FILION M, TREMBLAY L, DIPAOLO T, BEDARD PJ (1986) Effects of apomorphine on the spontaneous activity of the globus pallidus neurons in monkeys rendered parkinsonian by MPTP. *Abstracts of the Second Triennial Symposium of The International Basal Ganglia Society*, Victoria, British Columbia, Canada.

FRANKEL JP, LEES AJ, KEMPSTER PA, STERN GM (1990) Subcutaneous apomorphine in the treatment of Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **53**, 96–101.

GEARY WA, WOOTEN GF (1987) In vivo tracer studies of glucose metabolism, cerebral blood flow, and protein synthesis in naloxone precipitated morphine withdrawal. *Neurochemical Research*, **12**, 573–580.

GIRAULT JA, SPAMPINATO U, GLOWINSKI J, BESSON MJ (1986) *In vivo* release of [^{3}H]γ-aminobutyric acid in the rat neostriatum—II. Opposing effects of D1 and D2 dopamine receptor stimulation in the dorsal caudate putamen. *Neuroscience*, **19**, 1109–1117.

HALL H, KÖHLER C, GAWELL L (1985) Some in vitro receptor binding properties of [^{3}H]eticlopride, a novel substituted benzamide, selective for dopamine-D$_2$ receptors in the rat brain. *European Journal of Pharmacology*, **111**, 191–199.

HARRISON MB, WILEY RG, WOOTEN GF (1990) Selective localization of striatal D$_1$ receptors to striatonigral neurons. *Brain Research, Amsterdam*, **528**, 317–322.

KADEKARO M, CRANE AM, SOKOLOFF L (1985) Differential effects of electrical stimulation of sciatic nerve on metabolic activity in spinal cord and dorsal root ganglion in the rat. *Proceedings of the National Academy of Sciences of the USA*, **82**, 6010–6013.

KITAI ST, KITA H (1987) Anatomy and physiology of the subthalamic nucleus: a driving force of the basal ganglia. In. *The Basal Ganglia II: Structure and Function—Current Concepts. Advances in Behavioral Biology*, Volume 32. Edited by M. B. Carpenter and A. Jayaraman. New York and London: Plenum Press, pp 357–373.

KOHLER C, HALL H, ÖGREN S-O, GAWELL L (1985) Specific *in vitro* and *in vivo* binding of ^{3}H-raclopride: a potent substituted benzamide drug with high affinity for dopamine D-2 receptors in the rat brain. *Biochemical Pharmacology*, **34**, 2251–2259.

KOZLOWSKI MR, MARSHALL JF (1980) Plasticity of [^{14}C]2-deoxy-D-glucose incorporation into neostriatum and related structures in response to dopamine neuron damage and apomorphine replacement. *Brain Research, Amsterdam*, **197**, 167–183.

KOZLOWSKI MR, SAWYER S, MARSHALL JF (1980) Behavioural effects and supersensitivity following nigral dopamine receptor stimulation. *Nature, London*, **287**, 52–54.

LESLIE CA, BENNETT JP (1987) Striatal D$_1$- and D$_2$-dopamine receptor sites are separately detectable in vivo. *Brain Research, Amsterdam*, **415**, 90–97.

MATA M, FINK DJ, GAINER H, SMITH CB, DAVIDSEN L, SAVAKI H *et al.* (1980) Activity-dependent energy metabolism in rat posterior pituitary primarily reflects sodium pump activity. *Journal of Neurochemistry*, **34**, 213–215.

MELAMED E, HEFTI F, BITTON V, GLOBUS M (1984) Suppression of L-dopa-induced circling in rats with nigral lesions by blockade of central dopa-decarboxylase. implications for mechanism of action of L-dopa in parkinsonism. *Neurology, Cleveland*, **34**, 1566–1570.

MITCHELL IJ, CROSSMAN AR (1984) In defence of optical density ratios in 2-deoxyglucose autoradiography. *Brain Research, Amsterdam*, **298**, 191–192.

MITCHELL IJ, JACKSON A, SAMBROOK MA, CROSSMAN AR (1989) The role of the subthalamic nucleus in experimental chorea: evidence from 2-deoxyglucose metabolic mapping and horseradish peroxidase tracing studies. *Brain*, **112**, 1533–1548.

MOURADIAN MM, JUNCOS JL, FABBRINI G, SCHLEGEL J, BARTKO JJ, CHASE TN (1988) Motor fluctuations in Parkinson's disease: central pathophysiological mechanisms, Part II. *Annals of Neurology*, **24**, 372–378.

PARENT A, SMITH Y (1987) Differential dopaminergic innervation of the two pallidal segments in the squirrel monkey (*Saimiri sciureus*). *Brain Research, Amsterdam*, **426**, 397–400.

PAXINOS G, WATSON C (1982) *The Rat Brain in Stereotaxic Coordinates*. New York: Academic Press.

PORRINO LJ, BURNS RS, CRANE AM, PALOMBO E, KOPIN IJ, SOKOLOFF L (1987*a*) Local cerebral metabolic effects of L-dopa therapy in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in monkeys. *Proceedings of the National Academy of Sciences of the USA*, **84**, 5995–5999.

PORRINO LJ, PALOMBO E, BANKIEWICZ KS, KOPIN IJ (1987*b*) Anatomical specificity of the effects of L-DOPA in MPTP-induced hemiparkinsonism. *Society for Neuroscience Abstracts*, **13**, 1362.

RASCOL O, CLANET M, MONTASTRUC JL, SIMONETTA M, SOULIER-ESTEVE MJ, DOYON B *et al.* (1989) Abnormal ocular movements in Parkinson's disease: evidence for involvement of dopaminergic systems. *Brain*, **112**, 1193–1214.

RICHFIELD EK, YOUNG AB, PENNEY JB (1987) Comparative distribution of dopamine D-1 and D-2 receptors in the basal ganglia of turtles, pigeons, rats, cats, and monkeys. *Journal of Comparative Neurology*, **262**, 446–463.

ROBERTSON GS, ROBERTSON HA (1989) Evidence that L-dopa-induced rotational behavior is dependent on both striatal and nigral mechanisms. *Journal of Neuroscience*, **9**, 3326–3331.

Sharp FR, Kilduff TS, Bzorgchami S, Heller HC, Ryan AF (1983) The relationship of local cerebral glucose utilization to optical density ratios. *Brain Research, Amsterdam,* **263,** 97–103.

Snedecor GW, Cochran WG (1967) *Statistical Methods.* Sixth edition. Ames: Iowa State University Press, pp. 92–94.

Sokoloff L (1977) Relation between physiological function and energy metabolism in the central nervous system. *Journal of Neurochemistry,* **29,** 13–26.

Sonsalla PK, Manzino L, Heikkila RE (1988) Interactions of D1 and D2 dopamine receptors on the ipsilateral *vs.* contralateral side in rats with unilateral lesions of the dopaminergic nigrostriatal pathway. *Journal of Pharmacology and Experimental Therapeutics,* **247,** 180–185.

Trugman JM, Wooten GF (1986) The effects of L-DOPA on regional cerebral glucose utilization in rats with unilateral lesions of the substantia nigra. *Brain Research, Amsterdam,* **379,** 264–274.

Trugman JM, Wooten GF (1987) Selective D_1 and D_2 dopamine agonists differentially alter basal ganglia glucose utilization in rats with unilateral 6-hydroxydopamine substantia nigra lesions. *Journal of Neuroscience,* **7,** 2927–2935.

Ungerstedt U, Avemo A, Avemo E, Ljungberg T, Ranje C (1973) Animal models of parkinsonism. *Advances in Neurology,* **3,** 257–271.

Waddington JL, O'Boyle KM (1989) Drugs acting on brain dopamine receptors: a conceptual re-evaluation five years after the first selective D-1 antagonist. *Pharmacology and Therapeutics,* **43,** 1–52.

Walters JR, Bergstrom DA, Carlson JH, Chase TN, Braun AR (1987) D_1 dopamine receptor activation required for postsynaptic expression of D_2 agonist effects. *Science,* **236,** 719–722.

Waszczak BL, Lee EK, Tamminga CA, Walters JR (1984) Effect of dopamine system activation on substantia nigra pars reticulata output neurons: variable single-unit responses in normal rats and inhibition in 6-hydroxydopamine-lesioned rats. *Journal of Neuroscience,* **4,** 2369–2375.

Weick BG, Walters JR (1987) Effects of D_1 and D_2 dopamine receptor stimulation on the activity of substantia nigra pars reticulata neurons in 6-hydroxydopamine lesioned rats: D_1/D_2 coactivation induces potentiated responses. *Brain Research, Amsterdam,* **405,** 234–246.

Weick BG, Walters JR (1988) The D-1 selective agonist SKF 38393 can activate striatal neurons in 6-hydroxydopamine lesioned rats. *Society for Neuroscience Abstracts,* **14,** 1077.

Wooten GF, Collins RC (1981) Metabolic effects of unilateral lesion of the substantia nigra. *Journal of Neuroscience,* **1,** 285–291.

Wurtz RH, Hikosaka O (1986) Role of the basal ganglia in the initiation of saccadic eye movements. *Progress in Brain Research,* **64,** 175–190.

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HEMISPHERE ASYMMETRY IN DECISION MAKING ABILITIES

AN EXPERIMENTAL STUDY IN UNILATERAL BRAIN DAMAGE*

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SUMMARY

Thirty control subjects and 60 unilateral brain-damaged patients, 30 with left hemisphere (LH) damage and 30 with right hemisphere (RH) disease, underwent a disjunctive 4-choice reaction time study. *Speed* of reaction (as defined by the reciprocal of reaction time (RT), movement time (MT) and total response time (TRT)) and *accuracy* of response (as represented by the sum of errors in selecting the correct response key) were investigated comparatively as a function of side of lesion and of performance on Raven's Coloured Progressive Matrices (PM47). In contrast to movement speed (1/MT), reaction speed (1/RT) as well as total response speed (1/TRT) showed a lesion effect independent of side of damage. Conversely, accuracy was differentially impaired, LH damage being associated with a significantly higher number of errors. Speed and accuracy had different relationships with the performance on the PM47 in the two hemisphere groups. Speed was affected in parallel with changes in PM47 performance both in the LH and in RH groups, whereas accuracy was altered only in LH patients.

It was concluded that speed of motor reaction is affected by unilateral brain lesions irrespective of their side, whereas decision making processes, as expressed by accuracy of response, seem to be specifically impaired by LH damage.

INTRODUCTION

Performance on a multiple choice reaction time task may be defined both by accuracy of choice and speed of response. Whether these two variables are to be regarded as different aspects of the same mechanism(s), namely, decision making processes, or as separate cerebral functions, is currently unknown. Since decision making processes appear to be represented asymmetrically in the two cerebral hemispheres (Bisiach *et al.*, 1982; Riege *et al.*, 1982; Heister and Schroeder-Heister, 1984; Vallar *et al.*, 1984, 1988), this issue may conveniently be examined in patients with unilateral brain damage. Results from the study of brain-damaged patients also may be useful for interpreting studies of normal individuals using specialized reaction time (RT) procedures such as lateralized stimulus presentations and/or response choices.

Dee and Van Allen (1973) investigated the reaction time performances of patients

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with left (LH) and right (RH) unilateral cerebral disease using simple (1 choice), 2, 3 and 4-choice RT paradigms. They measured speed of reaction and accuracy of response. Both groups of patients with cerebral disease were significantly slower than controls. Furthermore, the two brain-damaged groups differed from each other in terms of the relationship between RT and task difficulty. In simple RT, when only one decision was implied, the speed of the LH and RH groups was equal. However, in the more demanding multiple-choice paradigms, the LH patients were significantly slower. Like the control group, both brain-damaged groups showed the 'complexity effect' as defined by Miller (1970) and Van Zomeren and Deelman (1978). In the Dee and Van Allen study (1973) reaction speed became progressively slower with increasing number of stimulus and response choices (e.g., passing from simple to 4-choice tasks). However, such a complexity effect was significantly greater in LH patients as compared with RH patients who, conversely, did not differ from controls. In both the hemisphere groups the 'complexity effect' was paralleled by a significant relation between the number and accuracy of choices (Dee and Van Allen, 1973). Errors in response selection were, indeed, significantly greater in the LH group as compared with the RH group and these differences increased with increasing task complexity. Thus while speed of reaction seemed to change concurrently with complexity of choice in both brain-damage groups, problems in decision making appeared to have a greater bearing on the performance of LH patients.

Such results seem to suggest that both accuracy and speed in RT reflect an impairment of the same decision making processes, and that these processes are more closely related to the integrity of the left hemisphere than the right (Bisiach *et al.*, 1982; Riege *et al.*, 1982; Heister and Schroeder-Heister, 1984; Vallar *et al.*, 1984, 1988). Thus, the effect of damage to the left hemisphere may be to produce greater uncertainty in decision making and this is manifested in both reduced accuracy and slower responses (Van Zomeren, 1981).

However, the reported close association between response accuracy and speed in patients with LH lesions (Dee and Van Allen, 1973) could have been coincidental because these authors only considered side of lesion while ignoring other functional characteristics that also may have differed between the groups. For example, the accuracy-speed relationship might be specifically determined by a third factor such as intellectual impairment. If intellectual impairment influences decision making accuracy as well as speed of response (Elsass and Hartelius, 1985; Elsass, 1986), then the stronger accuracy-speed relationship in the Dee and Van Allen LH patients might simply reflect the presence of greater intellectual deficits.

In view of these considerations we reexamined the effects of unilateral LH and RH lesions on the accuracy of choice and speed of response in a 4-choice RT task. Additionally, the results were analysed with respect to the level of intellectual functioning as assessed by Raven's Progressive Matrices (PM47) test. To exclude possible biases due to attentional defects, both warned and unwarned stimulus presentations were studied. This study sought to determine: (1) whether speed and accuracy are equally affected by side of lesion; (2) whether intrasubject changes in speed of reaction are related to accuracy of decision making; and (3) whether intellectual changes occurring in the two hemisphere groups affect both.

The Choice-RT task was performed with the hand ipsilateral to the lesion. In order to investigate the effect of hemisphere damage on ipsilateral control of complex motor sequences both the total response time, that is, the time needed to complete each 4-choice trial, and its constituent parts, namely, reaction time and movement time, were assessed. There is some evidence that reaction and movement times may have different relationships with decision making ability (Van Zomeren, 1981).

METHODS

Subjects

The investigation was carried out in 30 Control subjects and 60 unilateral brain-damaged patients. All were right handed. The Control subjects were without any past or present history of neurological or psychiatric disease and were inpatients of the Department of Internal Medicine of the University of Genoa. Since the brain-damaged patients had to perform the motor task with the hand ipsilateral to the side of their lesion, we first investigated the possible occurrence of a hand effect on the reaction (RT) and movement times (MT)—as defined below—of Control patients. Fifteen Controls were randomly selected to perform the task with the left hand and 15 with the right hand. These two groups did not differ with respect to age (t = 0.15, df 29, n.s.) and educational level (t = 1.5, df 29, n.s.). Because there was no hand effect on either RT (F = 0.70, df 1,28, n.s.) or MT (F = 1.2, df 1,28, n.s.), these 2 samples were combined into a single Control group.

From a series of consecutive patients admitted to the Department of Neurology of the University of Genoa in the period 1987 – 1988, 60 unilateral brain-damaged patients were selected for study who met the following criteria: (1) a clinical condition allowing the patient to keep the correct posture and to maintain attention for the entire length of the testing session, i.e., about 30 min; (2) right handedness as assessed by a translated version of the Neurosensory Center Handedness Questionnaire (Varney and Benton, 1975); (3) absence of signs of severe apraxia; and (4) CT scan evidence confirming the presence of a strictly unilateral cerebral lesion.

The brain-damaged subjects consisted of 30 patients with LH lesions and 30 with RH lesions. Fifteen of the patients in the LH group were classified as aphasic by both clinical observation and by performance on the Token Test (De Renzi and Faglioni, 1978); by the same criteria, no patient in the RH group was classified as aphasic. Visual field defects, assessed by the confrontation method or Goldmann kinetic perimetry, were present in 3 patients in the LH group and 7 patients in the RH group. The aetiology of the majority of lesions was vascular (LH: n = 20, RH: n = 16); in the remaining cases, the aetiology was neoplastic in nature. The test was given not earlier than 30 days from the estimated beginning of symptomatology.

There was no difference in age (F = 0.14, df 2,87, n.s.) among Controls (56.2 ± 8.9), LH patients (56.9 ± 8.2) and RH patients (55.7 ± 10.9). Likewise, there was no difference in educational level (F = 0.04, df 2,87, n.s.) among Controls (6.9 ± 3.9), patients with LH lesions (6.6 ± 3.6), and patients with RH lesions (6.7 ± 3.6). Colour vision, tested with Ishihara isochromatic plates, was within normal limits (De Renzi and Spinnler, 1967) in all the patients.

Clinical signs of impairment in motor, somatosensory and visual functioning at the time of admission were summarized by an *impairment rating* according to simple criteria reported elsewhere (Tartaglione *et al.*, 1986). This rating was used to monitor the severity of neurological disability. The maximum severity score of 100 corresponded to the simultaneous presence of the 3 defects at their highest level of gravity. The severity of aphasia was rated separately on the basis of the Token Test performance.

CT scans were performed on all brain-damaged subjects in the Neuroradiology Service of the Ospedale S. Martino of Genoa using a Hitachi A-TOM-X3576R scanner with a matrix of 512 × 512 points. The area of disease in each CT slice was defined by the largest extension of abnormal density in each image and consequently included both the lesion and surrounding oedema. The area of disease was then multiplied by the thickness of the slice to yield a measure of volume or size of lesion (McCullough *et al.*, 1979). The intrahemispheric distribution of lesions in the two hemisphere groups was assessed according to a previously established procedure (Mazzocchi and Vignolo, 1978; Tartaglione *et al.*, 1987). The method provides a numerical estimate of position of individual lesions, considering independently their superficial and deep extents as defined by Luzzatti *et al.* (1979).

Procedure

4-choice reaction time. All the patients participated in 2 sessions given on successive days. The patients, who were comfortably seated in a darkened room, fixated on a diffusely lit television screen placed at a distance of 107 cm. The stimuli (i.e., the imperative signals) were high luminance rectangles of different colours that subtended 7.7×5.3 deg of visual angle at the eye and were presented for a duration of 150 ms. The colours were white, yellow, blue and red. Stimulus luminance, measured with a Tektronik J4 photometer, were respectively: white = 39.3 cd/m^2, yellow = 37.3 cd/m^2, red = 36.8 cd/m^2, blue = 38.1 cd/m^2. The response keyboard presented a central grey button (reaction key) in front of the row of the 4 response keys which had the same colour as the stimuli. From left to right these were: yellow, red, blue and white. Each trial started by having the patient look at a central fixation point while holding down the reaction key with the hand ipsilateral to the lesion. The subjects were instructed to release the reaction key and to press the response key of the appropriate colour as quickly as possible after the delivery of the imperative signal. Two different modes of presentation were employed in each session. In the *warned mode* a low buzz preceded the imperative stimulus by a variable interval, i.e., 1.5, 2 or 2.5 s. The warning tone, which signalled to the patient to look at the fixation point and to press down on the reaction key, was expected to arouse attention at the initiation of each trial. In the *unwarned mode* stimuli followed each other without any warning at a variable interstimulus interval, i.e., 4, 5 or 6 s. Patients were instructed to return their hand to the reaction key immediately after each stimulus-response sequence. Pushing down the reaction key started the time of the events. Whenever a patient failed to release the reaction key within 4 s from the presentation of the imperative signal in both the warned and unwarned procedures, the trial was considered a 'lapse' and discarded. RTs shorter than 150 ms were considered 'false alarms' and also were discarded. In both cases the trials were recorded and repeated later in the same session.

On the basis of the data of Hamsher and Benton (1977), both in the first and in the second session, 2 blocks of 36 trials each were given, one using the warned presentation (W blocks) and the other the unwarned presentation (UW blocks), totalling 144 trials in the two sessions. Intervals between warning and imperative stimuli in case of W blocks and interstimulus intervals in case of UW blocks were predetermined so that: (1) the same interval did not occur twice in a row; (2) each interval occurred an equal number of times in all the blocks. Furthermore, in order to counterbalance the possible existence of carry-over effects associated with learning or fatigue, the W block was given before the UW block in half the patients, while in the other half the order of blocks was reversed. Each block was preceded by a series of 10 practice trials. A TV circuit monitored whether the patient was fixating the central rod on the screen correctly and using the RT key properly. Whenever patients failed to maintain this fixation, the block was interrupted and the patient allowed to rest.

The colours were equiprobable as each stimulus colour occurred an equal number of times in each block, i.e., 9 times, totalling 36 replications in the 4 blocks. The same colour was never presented twice in a row.

Errors and speed were recorded in all the trials.

Attentional errors. 'Lapses' and 'false alarms', referred to as *attentional errors*, were determined within each session. The between-session difference was tested in each group employing the Friedman two-way analysis of variance. The difference was not significant either in normal Controls (χ^2 = 1.7, df 1, n.s.) or in brain-damaged patients (LH group; χ^2 = 0.6, df 1, n.s.; RH group: χ^2 = 0.9, df 1, n.s.). Individual results were therefore summed to yield an *overall score* which was entered into the statistical analysis.

Selection errors. The apparatus automatically recorded whether the selected response key was correct, i.e., had the same colour as the stimulus. Correct responses were coded 0 and errors 1. This between-session difference, tested in each group by employing the Friedman two-way analysis of variance, was not significant either in the normal Controls (χ^2 = 2.7, df 1, n.s.) and in brain-damaged patients (LH group: χ^2 = 0.01, df 1, n.s.; RH group: χ^2 = 0.533, df 1, n.s.). Individual results were therefore summed to yield an *overall error score* to which the analysis will refer.

Speed. In each trial, 3 values were automatically recorded: (1) *reaction time* (RT), i.e., the elapsed time between the delivery of the stimulus and release of the reaction key; (2) *movement time* (MT), i.e., the elapsed time between release of the reaction key and pressing of the response button; and (3) *total response time* (TRT), i.e., the sum of RT and MT which corresponded to the elapsed time between the delivery of the stimulus and pressing the response button.

The reciprocal of the time in seconds for RT, MT and TRT was calculated and recorded on each trial. For example, a time of 250 ms would correspond to a transformed value of 4, which gives a measure of speed. Such a transformation was carried out so as to reduce the heterogeneity of variance between the Control and brain-damaged groups. Median values of RT, MT and TRT were computed for each block of trials so that at the end of the two sessions individual performances were defined by 4 medians for each of the 3 measures.

A mixed design analysis of variance was carried out to determine whether the session factor interfered with performance. For this analysis, group (i.e., Control vs LH and RH groups) was treated as the between-subject factor; session (first vs second) and mode of presentation (warned vs unwarned) were the within-subject factors. The interaction between group and session was not significant for either RT (F = 0.48, df 2,87; n.s.) or MT (F = 0.05; df 2.87; n.s.), indicating that the performances of the three groups did not change across the two sessions. Therefore, the medians of warned and unwarned blocks of trials performed in the two sessions were separately averaged and the means employed in subsequent data analysis.

Raven's coloured progressive matrices (PM47). The PM47 book form has 36 incompletely coloured designs and 6 alternatives, only 1 of which correctly completes the main design. Patients were instructed to select the correct alternative. No time limits were imposed. Since norms for Italian adults (Basso *et al.*, 1987) were not available at the beginning of this investigation a preliminary study was carried out on an independent group of 259 Control patients who were without a past or present history of neurological or psychiatric disease. These subjects were randomly selected from the Department of Internal Medicine of the University of Genoa. In keeping with previous data, we found that educational level and age affected individual results. For the development of normative standards, the subjects were subdivided into three educational groups: Group A: 0–3 yrs of education; Group B: 4–5 yrs of education; Group C: more than 5 yrs of schooling. Within Group A, age had no effect on performance level, whereas it influenced the level of performance in Group B and C. These 2 groups were further subdivided into 2 subgroups. Groups B1 and B2 represented, respectively, the subjects at or below age 60 and those above age 60 yrs. Groups C1 and C2 represented the subjects at or below age 65 and those above age 65 yrs, respectively.

To allow a comparison of the performance of brain-damaged patients independent of the effects of educational level and age on PM47, each score was transformed into its corresponding percentile according to the distributions reported above.

RESULTS

A. Severity of clinical impairment—size and site of brain damage

The mean impairment rating for the severity of neurological deficits did not differ (t = 1.5, df 58; n.s.) between LH (mean = 30.8, SD = 21.6) and RH (mean = 23.3, SD = 19.5) groups.

The means of lesion volume (in arbitrary units) were 51.9 (SD = 50.4) in the LH group and 69.1 (SD = 55.7) in the RH group. This difference did not reach the 0.05 level of significance (t = 1.23, df 58, n.s.).

There was no significant difference between the two hemisphere groups with respect to the intrahemispheric localization of lesions, both in their superficial (χ^2 = 1.5; df 2, n.s.) and deep extents (χ^2 = 0.6, df 2, n.s.).

The lack of differences between LH and RH groups, so far as severity of clinical impairment, size and site of brain damage are concerned, thus provided an unbiased comparison of their performances.

B. 4-choice reaction time performance

Speed of response

Table 1 shows the means and SDs of individual transformed medians of RT, MT, TRT, i.e., reaction speed (RS), movement speed (MS) and total response speed (TRS), relative to the three groups of patients. Each variable was separately investigated by a mixed design of analysis of variance (ANOVA) (Winer, 1971) with group (Controls, LH and RH groups) as the between-subject factor and mode of presentation (warned and unwarned mode) as the within-subject factor. The ANOVA summaries corresponding to each variable are given in Table 1.

TABLE 1 ANALYSIS OF REACTION SPEED, MOVEMENT SPEED AND TOTAL RESPONSE SPEED*

	Reaction speed		*Movement speed*		*Total response speed*	
	W	*UW*	*W*	*UW*	*W*	*UW*
Controls	2.34±0.43 (427)	2.19±0.36 (457)	3.19±0.70 (312.2)	3.45±0.94 (289.9)	1.29±0.14 (775)	1.27±0.13 (784.9)
LH group	1.95±0.54 (512)	1.95±0.58 (512)	2.71±1.11 (368.9)	2.69±1.04 (372.1)	1.08±0.31 (929.6)	1.07±0.32 (933.8)
RH group	1.85±0.55 (541)	1.84±0.44 (543)	2.99±1.20 (334.1)	2.95±1.19 (338.9)	1.13±0.33 (881.7)	1.05±0.28 (945.3)

ANOVA tables

	SS	*df*	*F*	*SS*	*df*	*F*	*SS*	*df*	*F*
Groups (A)	5.73	2	6.39***	11.67	2	2.8	1.56	2	6.06***
Error	39.03	87		178.2	87		11.24	87	
Mode (B)	0.15	1	4.7**	0.18	1	1.28	0.046	1	5.11***
(A)×(B)	0.213	2	3.4**	0.84	2	2.98	0.044	2	2.44
Error	2.687	87		12.266	87		0.768	87	

* Means and SDs deviations of individual speed in control, LH and RH groups for warned (W) and unwarned (UW) mode of presentation. Speed is the reciprocal of single times (×1000). Individual speed is obtained by averaging the medians of two blocks of trials The values in brackets are times (in ms) derived from the corresponding mean speed. ** $P < 0.05$; *** $P < 0.01$. SS = sum of squares

For RS there was a significant effect of the group factor. Comparisons of the group means by the Neuman-Keuls method indicated that Controls were faster than both LH ($q = 5.51, P < 0.01$) and RH patients ($q = 6.88, P < 0.01$), while the brain-damaged groups did not differ from each other ($q = 1.77$, n.s.). A slight tendency for reaction to be faster in warned compared with unwarned presentations was apparent in the Control group and yielded a significant interaction between mode of presentation and group. As it will be shown, such a tendency applies to the TRS of all the groups, though to variable degrees.

For MS, neither the group nor mode of presentation, nor their interaction were significant.

For TRS both group and mode of presentation had a significant effect on performance. Comparison of means by the Neuman-Keuls method indicated that the Control group was faster than the LH ($q = 4.99, P < 0.01$) and RH ($q = 3.99, P < 0.01$) groups, while the latter two did not differ from each other ($q = 0.49$, n.s.). The significant effect of mode of presentation reflected the slight tendency to react faster in warned presentations than in unwarned ones.

Accuracy of performance

Means of both selection and attentional errors for the three groups are reported in fig. 1.

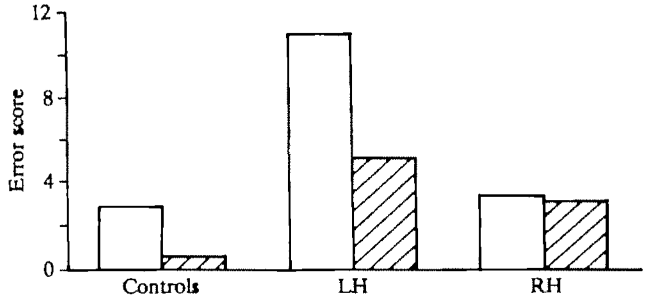

FIG. 1 Mean values of selection (open bars) and attentional (hatched bars) errors in Control, LH and RH groups.

Selection errors. The Kruskal-Wallis analysis of variance amongst groups was significant ($\chi^2 = 6.38$, $P < 0.05$). LH patients performed significantly worse than Control patients (Mann-Whitney: $Z = -1.92$, $P = 0.05$) and RH patients (Mann-Whitney: $Z = -2.31$, $P = 0.02$), while RH patients did not differ from Controls (Mann-Whitney: $Z = -0.75$, $P = 0.45$).

Errors and perseveration. The possibility that selection errors depended on a tendency to perseverate, that is, to keep on pressing the same key, was indirectly assessed in inaccurate performers of both hemisphere groups. A series of 3 or more errors in a row was considered as a possible expression of perseveration. Although this definition was forcedly extensive (as the key selected in case of error was not known), only 3 patients in the LH group presented 'perseverative errors' (2 patients once and 1 twice) while no patient did in the RH group. Such figures are too small to infer a meaningful contribution of perseveration, if any, in differently impairing the performance of the two hemisphere groups.

Accuracy. The level of accuracy, defined as the number of selection errors made by each individual throughout the blocks of trials, was determined relative to the cut-off value of normal performances. As scores in the control group had a Poisson distribution, the data (x) were preliminary normalized by transforming them into square roots (SQRT), that is, $\mathrm{SQRT}(x) + \mathrm{SQRT}(x+1)$ (Lentner, 1982). The cut-off, i.e., the 95th percentile estimated from SQRT values, corresponded to a raw score of 6.3: 14 patients (46.7%) in the LH group surpassed this level as opposed to 6 patients (20%) in the RH group. These patients will be referred to as *inaccurate performers*; further analysis in this section will specifically take into account their performance, while ignoring that of the *normal or accurate performers*. The mean error scores and SD of these patients were respectively 22.5 ± 14.9 in the LH group and 11.0 ± 6.8 in the RH one. This difference was significant ($t = 3.86$, df 18, $P < 0.01$).

Relationship between selection and attentional errors. The Kruskal-Wallis analysis of variance of attentional errors (*see* fig. 1) was significant ($\chi^2 = 13.73$, $P = 0.001$). The Mann-Whitney test showed that LH as well RH patients were significantly worse than Controls (LH vs Control group: $Z = -3.23$, $P = 0.001$; RH vs Control group: $Z = -3.31$, $P = 0.001$). However, LH and RH groups did not differ from each other ($Z = -0.43$, $P = 0.66$).

Means and SD of attentional errors in accurate and inaccurate LH patients were, respectively, 5.47 ± 7.1 and 4.54 ± 7.6. The difference was not significant (Mann-Whitney: $Z = -0.11$; n.s.). The corresponding data in accurate and inaccurate RH patients were, respectively, 2.4 ± 1.5 and 6.6 ± 5.4. The difference was significant ($Z = -1.96$, $P < 0.05$).

Errors as a function of stimulus/response conditions. The question was raised as to whether selection errors were randomly distributed across the 4 stimulus/response conditions. Frequencies of correct responses and errors were determined as a function of the stimulus colour in Control patients, inaccurate LH performers and inaccurate RH performers. These data are cross-tabulated in Table 2.

TABLE 2. FREQUENCIES OF CORRECT RESPONSES AND ERRORS AS A FUNCTION OF THE STIMULUS IN NORMAL CONTROLS (A), INACCURATE LH PATIENTS (B), INACCURATE RH PATIENTS (C)*

	A. Colours				*B. Colours*				*C. Colours*			
	Yellow	*Red*	*Blue*	*White*	*Yellow*	*Red*	*Blue*	*White*	*Yellow*	*Red*	*Blue*	*White*
Correct	1071	1066	1040	1052	412	367	377	422	175	168	162	158
(%)	99.2	98.7	96.3	97.4	88.8	78.9	80.0	89.6	96.7	94.9	90.0	87.8
Errors	9	14	40	28	52	98	94	49	6	9	18	22
(%)	0.8	1.3	3.7	2.6	11.2	21.1	20.0	10.4	3.3	5.1	10.0	12.2

* Percentages (%) refers to column totals.

Hierarchical log-linear analysis

	df	χ^2	*P*
Main factors	6	10765.4	< 0.001
Group	2	2983.9	< 0.001
Colour	3	0.4	0.99
Response	1	6308.5	< 0.001
Two-way interaction	11	470.6	< 0.001
Group × response	2	376.4	< 0.001
Group × colour	6	2.0	0.91
Response × colour	3	40.1	< 0.001
Three-way interaction	6	34.9	< 0.001

The performances of the three groups were analysed according to a log-linear model (Norušis, 1986; Clogg and Shockley, 1988). Group (Controls, inaccurate LH performers and inaccurate RH performers), colour (white, yellow, red and blue) and response (correct, incorrect) were the factors. The significant three-way interaction (Table 2) suggests that errors were not at random, their distribution differing in the three groups as a function of stimulus/response condition. The triple interaction was significant also when the individual comparisons of LH patients vs Controls ($\chi^2 = 22.29$, $P < 0.01$) and vs RH patients ($\chi^2 = 19.02$, $P < 0.01$) were separately considered. However, it was not when Controls were compared with RH patients ($\chi^2 = 2.04$, n.s.). This suggests that the latter two groups were characterized by a similar distribution of errors, both differing from LH patients. As shown in Table 2, where colours are reported in the same spatial order (from left to right) that they have in the keyboard, in Controls and in RH patients errors were relatively higher when the rightmost buttons (blue and white) were to be selected, whereas, in LH patients they were mostly found when central buttons (red and blue) had to be chosen.

Influence of error on speed. Individual RS, MS and TRS medians were separately computed for correct responses and errors of inaccurate LH and RH performers. For each group individual data were separately entered in a multivariate design of analysis of variance (Norušis, 1986) with two within-subjects factors, namely, error (correct vs incorrect responses) and variable (RS, MS, TRS). The averaged medians of all the conditions are given in fig. 2A for the inaccurate LH and in fig. 2B for the inaccurate RH patients.

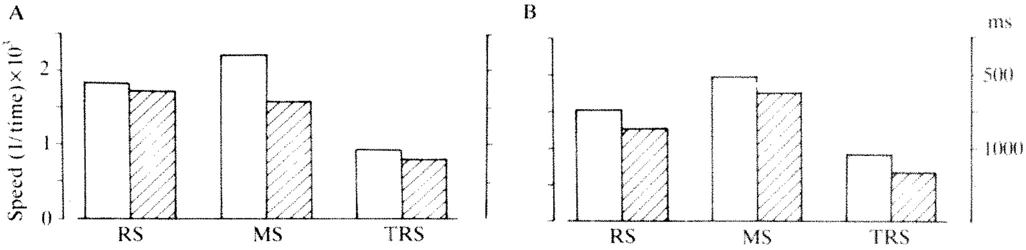

FIG. 2. Mean speed values of correct responses (open bars) and errors (hatched bars) in LH (A) and RH (B) inaccurate performers. The parameters are, respectively, response speed (RS), movement speed (MS) and total response speed (TRS).

Error proved to be significant both in the inaccurate LH (F = 8.75, df 1,12, $P = 0.012$) and RH (F = 11.61, df 1,4, $P = 0.027$) patients. In both groups errors were associated with a consistent slowing of speed which affected all the variables (RS, MS, TRS). The result was particularly apparent in LH patients, where MS changes were so large as to yield a significant interaction between error and this variable (approx. F = 4.8, df 2,11, $P < 0.05$).

Accuracy and speed

The frequency of abnormal accuracy, corresponding to an error score greater than 6.3, was compared with that for abnormal speed in both hemisphere groups. The estimate of velocity was based on TRS, the individual score being defined as the mean of 4 block medians. The normal cut-off score of speed, i.e., the fifth percentile of the Controls' performance, corresponded to a speed of $1.06 \cdot s^{-1}$, i.e., to a TRT of 941 ms. Speed falling below this value was considered abnormal. Fifteen patients (50%) in the LH group presented an abnormal speed compared with 13 patients (43.3%) in the RH group. The difference was not significant ($\chi^2 = 0.01$, df 1, n.s.).

The histograms in fig. 3 denote the percentage incidence of abnormal speed and of abnormal accuracy in the LH and RH groups. In contrast to RH patients, where inaccurate performances were rarer (20%) than abnormally slow responses (43.3%), in the LH patients the frequency of inaccurate performances (46.7%) matched that of abnormally slow responses (50%). The question was therefore raised as to whether in the LH group speed and accuracy might have a parallel behaviour in single patients, a slower speed being associated with an inaccurate performance. Data are cross-tabulated in Table 3.

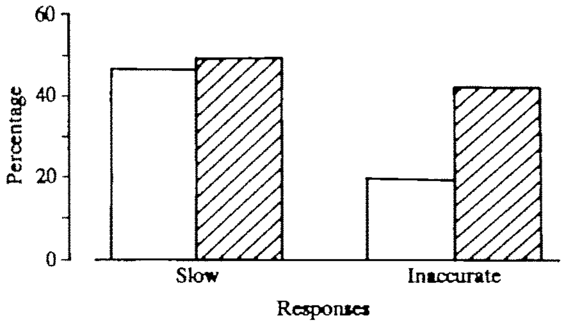

FIG. 3. Percentage incidence of slow responses (as defined by total response speed) and of inaccurate performances in RH (open bars) and in LH (hatched bars) groups.

TABLE 3. RELATIONSHIP BETWEEN SPEED OF REACTION AND ACCURACY OF RESPONSE

	LH Group			*RH Group*		
	Speed			*Speed*		
	Normal	*Abnormal*	*Total*	*Normal*	*Abnormal*	*Total*
Accuracy						
Normal	9	7	16	15	9	24
Abnormal	6	8	14	2	4	6
	15	15		17	13	

Seven (46.7%) of 15 LH patients responding with abnormal speed, presented a normal accuracy, and 6 (42.8%) of 14 LH patients performing with abnormal accuracy presented a normal speed. The McNemar test was not significant (χ^2 = 0.31, df 1, n.s.) indicating that there was no association between the level of accuracy and speed, nor was this test significant in the RH group (χ^2 = 0.10, df 1, n.s.).

C. 4-choice performance versus PM47 data

On the PM47, the mean scores were 28.1 (SD = 4.3) in the Control group, 21.5 (SD = 7.3) in the LH group and 22.77 (SD = 5.58) in the RH group. After transformation of individual results into percentiles, the means were 62.5 (SD = 25.2) in the Control group, 36.9 (SD = 31.8) in LH patients and 43.37 (SD = 31.8) in RH patients. A one-way analysis of variance indicated a significant effect both for the raw scores (F = 3.76, df 2,87, $P < 0.05$) and the percentiles (F = 4.05, df 2,87, $P < 0.05$). While the performance of the Control group was superior to that of the LH and RH groups, the performance of the two brain-damaged groups did not differ from each other either in terms of the raw scores (t = 1.03, df 58, n.s.) or of the percentiles (t = 0.81, df 58, n.s.).

The correlation between individual speed and PM47 performance was determined as shown in fig. 4, where LH data are presented in section A and RH data in section B. Log-transformed values of speed and PM47 percentiles were employed in order to meet the assumption of the test. The correlation coefficients were r = 0.56 in the LH group

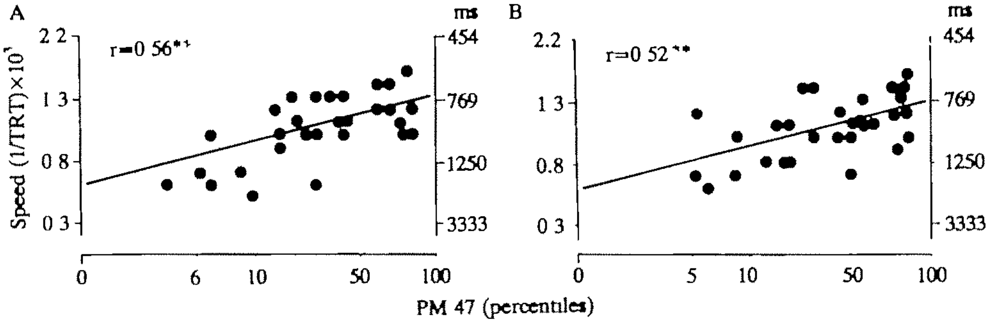

FIG. 4. Correlation between speed and performance (expressed in percentiles) on the Raven's Coloured Progressive Matrices (PM47) in the LH (A) and in the RH (B) groups. The data are reported in a log-log scale and the line corresponds to the best fit; the right-hand log scale presents the corresponding total response time. (**$P < 0.01$.)

($P = 0.003$) and r = 0.52 in the RH group ($P = 0.006$), suggesting that the relationship did not differ in the two hemisphere groups. The linear relationship accounts respectively for 31% and 27% of speed variance in LH and RH groups. The comparison of correlation coefficients after Z transform resulted in a nonsignificant difference (Z = 0.20).

In fig. 5, error scores were correlated with PM47 percentiles after a log transformation of individual values. LH data are presented in section A and RH data in section B. The correlation coefficients were r = −0.53 ($P = 0.002$) in the LH group and r = −0.03 (n.s.) in the RH group. The comparison of correlation coefficients after Z transform resulted in a significant difference (Z = 2.05, $P < 0.05$).

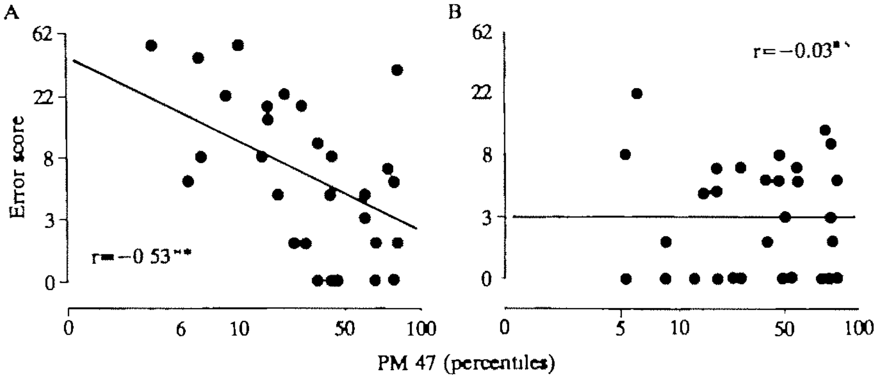

FIG. 5. Correlation between accuracy (as defined by the individual error score) and performance (expressed in percentiles) on the Raven's Progressive Coloured Matrices (PM47) in the LH (A) and in the RH (B) groups. The data are reported in a log-log scale and the line corresponds to the best fit. (**P 0.01)

Effect of aphasia. To address the question as to whether aphasia might be responsible for the parallel impairment of PM47 performance and accuracy in LH patients, aphasic and nonaphasic LH patients were compared as a function of these two measures. The

15 LH aphasic patients and 15 LH nonaphasic patients did not differ as a function of PM47 results (t = 1.27, df 28, n.s.); the mean PM47 percentile was 31.3 (SD = 32) in aphasics and 41.4 (SD = 31.29) in nonaphasics. In terms of accuracy, there was no difference (t = 0.02, df 28, n.s.) between the error scores of aphasic LH patients (mean = 9.3, SD = 12.6) and nonaphasic LH patients (mean = 9.1, SD = 12.1).

DISCUSSION

In order to establish whether and to what extent selection errors are related to impairment of decisional ability, it is necessary to exclude the possibility that other defects are implied by this type of error. The role of perceptual deficits could easily be dismissed in so far as our patients had no problems in colour perception, nor could their performance be influenced by the luminance of stimuli which was held constant in all the conditions. Moreover, our data seem to exclude errors due to perseveration, as the very rare 'perseverative errors' were found in only a few patients. The impaired performance might have depended on sensorimotor defects, responsible for a misreaching of the response keys. In addition, memory disturbances might have influenced the response by interfering with the recall of the colour of the stimulus. However, in both instances, randomly distributed errors would have been expected which, conversely, varied as a function of the response key position, possibly due to an abnormal enhancement of orientational tendencies (Takala, 1951; Taylor, 1961; Tartaglione *et al.*, 1981, 1983) to be discussed below.

The performance of our brain-damaged patients was characterized by the loss of trade-off normally relating correctness and speed of response. In normal subjects errors are associated with a significantly faster reaction speed than that of correct responses, suggesting that the error mainly reflect rash decisions (Franzon and Hugdahl, 1987). In our brain-damaged patients the significant retardation concomitant with errors seems to witness the presence of a high degree of uncertainty in choice, namely, a weakening of decisional capacity. Uncertainty characterized selection errors independently of side of lesion and caused a significant reduction of the total response speed.

Indecision caused orientational tendencies, weakly present in normals, to emerge. These affected the distribution of errors. In keeping with a general trend (Takala, 1951; Tartaglione *et al.*, 1983), the incidence of errors in our controls was greater when the choice was to be made on the right side of the keyboard. In inaccurate RH patients such a left-right gradient was maintained, whereas LH damage altered it, introducing new orienting references, as described elsewhere (Taylor, 1961; Tartaglione *et al.*, 1981). Indeed, performance in LH patients seemed mostly 'anchored' to the lateral keys where errors were less frequent than in the central ones. These results were maintained irrespective of visual field defects, the latter being present only (but not exclusively) in a few inaccurate patients.

Individual accuracy, as expressed by the overall error scores, was differentially affected in the two hemispheric groups, indicating that the cerebral hemispheres have a different bearing on decisional capacities. Decision making processes seemed to be significantly more impaired with LH disease than with RH disease. At variance with the LH patients, in the RH group inaccurate performances showed a high incidence of attentional errors.

Such an association indicates that the impairment of decisional ability might be related, at least partly, to the attentional defect. TRS did not differ between the two hemisphere groups, both being significantly slower than the Control group. This outcome depended uniquely on RS changes as MS was not significantly affected by brain damage (*see also* Van Zomeren, 1981). Thus in the RH group the behaviour of speed was obviously dissociated from that of accuracy. In the LH group, the frequency of inaccurate performances matched that of slow responses, thus suggesting a concurrent impairment of speed and accuracy. This was not in fact the case as almost half the inaccurate performers presented normal velocity and vice versa. It follows that speed of reaction and accuracy of response can be independently affected by a lesion, irrespective of its side.

Studies in brain-damaged patients (Dee and Van Allen, 1973) and in normal subjects (Bisiach *et al.*, 1982; Riege *et al.*, 1982; Heister and Schroeder-Heister, 1984; Vallar *et al.*, 1984, 1988) have suggested the presence of left hemisphere specialization for decision making processes. Such a functional asymmetry seemed to be confirmed by choice-RT investigations in normal subjects showing that left hemisphere activation produces a faster response than it does on the right (Bisiach *et al.*, 1982). In our study the existence of a hemisphere specialization for decision making processes found support in the symmetric impairment of response accuracy but not of its speed. This would negate the possibility that changes in accuracy of response and in speed of reaction can be accounted for by the impairment of a single mechanism. In particular, motor response planning, as estimated by velocity of reaction, seems independent of impairment in decisional mechanisms.

PM47 performance was equally affected in the two hemisphere groups, in keeping with other reports (Costa and Vaughan, 1962; De Renzi and Faglioni, 1965; Colonna and Faglioni, 1966; Basso *et al.*, 1973; Zaidel *et al.*, 1981). Although speed of motor reaction was positively and linearly correlated with PM47 performance in both LH and RH groups, as already suggested (Elsass and Hartelius, 1985; Elsass, 1986), only about 30% of the speed variance could be accounted for by performance on the PM47. In fact, independent researchers have reported that reaction time can also be normal in the presence of a very defective PM47 performance (Basso *et al.*, 1973). Alternatively, abnormal RTs can be associated with very mild defects in higher mental function (Jones *et al.*, 1989). All these data indicate that intellectual deficit and retardation of motor reaction are weakly correlated with each other in brain disease. This slight relationship might be accounted for by a 'general effect' of lesion on both types of performance (Benton and Joynt, 1959; De Renzi and Faglioni, 1965), thus suggesting that a slight difference in magnitude of such a general effect in the two hemisphere groups could be responsible for the different impairment of choice-RT in LH and RH patients, previously reported by Dee and Van Allen (1973).

The relationship of PM47 performance to individual accuracy differed depending on the side of the lesion. In the RH group few patients presented an abnormal level of accuracy which was independent of PM47 results. In LH patients accuracy varied in parallel with the intellectual defect both in aphasic and nonaphasic patients. In fact, the majority (71.4%) of inaccurate LH patients had low PM47 results (below the 25th percentile). Thus while damage to either hemisphere resulted in impairment of PM47, only in the left hemisphere was this impairment frequently associated with an abnormal level of accuracy in choice-RT. It should be pointed out that both tasks, although making different demands, imply a choice. Hence the postulated effect of a LH lesion in decision making processes might explain the concurrent defect often observed in the two types of performance. On the contrary, the impairment of PM47 performance in the RH group might be accounted for by a different functional defect (*see* Zaidel *et al.*, 1981), perhaps related to spatial cognition (Joynt and Goldstein, 1975; Newcombe and Ratcliffe, 1989). If this were the case, no relationship between accuracy and PM47 performance should be expected, assuming that cognitive abilities called for by PM47 performance are not implied in choice-RT.

Data from investigations in unilateral brain-damaged (Vaughan and Costa, 1962; Wyke, 1971; Brodal, 1973; Haaland *et al.*, 1977, 1987; Haaland and Delaney, 1981; Jones *et al.*, 1989) have indicated that each cerebral hemisphere participates in ipsilateral motor control, particularly for complex distal movements under continuous sensory feed-back (Haaland *et al.*, 1987; Jones *et al.*, 1989) as well as of those involving proximal arm segments (Di Stefano *et al.*, 1980; Jones *et al.*, 1989). Our data confirmed that hemisphere damage affects the movements of the arm ipsilateral to the lesion. However, contrary to expectations, the impairment did not involve MS, mainly depending on proximal segments of arm, but affected RS which relies on a simple distal movement. Such a dissociated impairment should exclude the possibility that retardation of response is due to a purely motor component, namely bradykinesia, which would affect both RS and MS. In fact, our data suggest that the lengthening of ipsilateral motor response reflects a 'sluggishness to react', perhaps due to a systematic difficulty in planning sensorimotor sequences (Jones *et al.*, 1989).

It has been observed that in head-injured patients there is a strong relationship between severity of damage and lengthening of RT (Van Zomeren and Deelman, 1976, 1978; Van Zomeren, 1981). Such an observation seems to confirm the hypothesis according to which the RT lengthening depends on the impairment of 'general capacities', as attention, that are especially needed in high speed performances (Blackburn and Benton, 1955; Benton and Joynt, 1959). However, this could hardly explain why RS and MS are differently impaired in our patients. To clarify this issue the possible role of factors such as the localization of intrahemispheric damage and/or its interaction with the volume of the lesion (Boller *et al.*, 1970; Howes and Boller, 1975; Tartaglione *et al.*, 1986, 1987) should be further investigated.

In summary, this study was concerned with the effects of unilateral brain damage on accuracy and speed in a 4-choice reaction time task. Accuracy was affected differently depending on the side of the lesion and this finding was in keeping with the asymmetry of decision making processes found in normal subjects. On the contrary, total response time, which included reaction time and movement time, was equally affected by LH and RH lesions. These data and the different relations between accuracy and speed of response with PM47 performance in the two unilateral brain-damaged groups indicate that accuracy and speed rely on independent mechanisms. It is therefore concluded that unilateral brain lesions in either hemisphere have the general effect of retarding the speed of reaction while lesions of the left hemisphere may have the more specific and additional effect of impairing decision making processes. At variance with the original hypothesis of Dee and Van Allen (1973), the impairment of decision making processes, per se, does not seem to affect speed of motor response.

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REFERENCES

BASSO A, DE RENZI E, FAGLIONI P, SCOTTI G, SPINNLER H (1973) Neuropsychological evidence for the existence of cerebral areas critical to the performance of intelligence tasks. *Brain*, **96**, 715–728.

BASSO A, CAPITANI E, LAIACONA M (1987) Raven's Coloured Progressive Matrices: normative values on 305 adult normal controls. *Functional Neurology*, **2**, 189–194.

BENTON AL, JOYNT RJ (1959) Reaction time in unilateral cerebral disease. *Confinia Neurologica*, **19**, 247–256.

BISIACH E, MINI M, STERZI R, VALLAR G (1982) Hemispheric lateralization of the decisional stage in choice reaction times to visual unstructured stimuli. *Cortex*, **18**, 191–197.

BLACKBURN HL, BENTON AL (1955) Simple and choice reaction time in cerebral disease. *Confinia Neurologica*, **15**, 327–338.

BOLLER F, HOWES D, PATTEN DH (1970) A behavioral evaluation of brain-scan estimates of lesion size. *Neurology, Minneapolis*, **20**, 852–859.

BRODAL A (1973) Self-observations and neuro-anatomical considerations after a stroke. *Brain*, **96**, 675–694

CLOGG CC, SHOCKLEY JW (1988) Multivariate analysis of discrete data. In: *Handbook of Multivariate Experimental Psychology*. Second edition. Edited by J. R. Nesselroade and R. B. Cattell. New York: Plenum Press, pp. 337–365.

COLONNA A, FAGLIONI P (1966) The performance of hemisphere-damaged patients on spatial intelligence tests. *Cortex*, **2**, 293–307.

COSTA LD, VAUGHAN HG (1962) Performance of patients with lateralized cerebral lesions. I: Verbal and perceptual tests. *Journal of Nervous and Mental Disease*, **134**, 162–168.

DEE HL, VAN ALLEN MW (1973) Speed of decision-making processes in patients with unilateral cerebral disease. *Archives of Neurology, Chicago*, **28**, 163–166.

DE RENZI E, FAGLIONI P (1965) The comparative efficiency of intelligence and vigilance tests in detecting hemispheric cerebral damage *Cortex*, **1**, 410–433.

DE RENZI E, SPINNLER H (1967) Impaired performance on color tasks in patients with hemispheric damage. *Cortex*, **3**, 194–217.

DE RENZI E, FAGLIONI P (1978) Normative data and screening power of a shortened version of the Token Test. *Cortex*, **14**, 41–49.

DI STEFANO M, MORELLI M, MARZI CA, BERLUCCHI G (1980) Hemispheric control of unilateral and bilateral movements of proximal and distal parts of the arm as inferred from simple reaction time to lateralized light stimuli in man. *Experimental Brain Research*, **38**, 197–204.

ELSASS P (1986) Continuous reaction times in cerebral dysfunction. *Acta Neurologica Scandinavica*, **73**, 225–246.

ELSASS P, HARTELIUS H (1985) Reaction time and brain disease: relations to location, etiology and progression of cerebral dysfunction. *Acta Neurologica Scandinavica*, **71**, 11–19.

FRANZON M, HUGDAHL K (1987) Effects of speed vs accuracy in vocal reaction time to visual half-field presentations of incongruent (Stroop) color-words. *Cortex*, **23**, 615–629.

HAALAND KY, CLEELAND CS, CARR D (1977) Motor performance after unilateral hemisphere damage in patients with tumor. *Archives of Neurology, Chicago*, **34**, 556–559.

HAALAND KY, DELANEY HD (1981) Motor deficits after left or right hemisphere damage due to stroke or tumor. *Neuropsychologia*, **19**, 17–27.

HAALAND KY, HARRINGTON DL, YEO R (1987) The effects of task complexity on motor performance in left and right CVA patients. *Neuropsychologia*, **25**, 783–794.

HAMSHER K DES, BENTON AL (1977) The reliability of reaction time determinations. *Cortex*, **13**, 306–310.

HEISTER G, SCHROEDER-HEISTER P (1984) A note on location of the decisional stages of choice reactions in the left hemisphere. *Cortex*, **20**, 271–275.

HOWES D, BOLLER F (1975) Simple reaction time: evidence for focal impairment from lesions of the right hemisphere. *Brain*, **98**, 317–332.

JONES RD, DONALDSON IM, PARKIN PJ (1989) Impairment and recovery of ipsilateral sensory-motor function following unilateral cerebral infarction. *Brain*, **112**, 113–132.

JOYNT RJ, GOLDSTEIN MN (1975) Minor cerebral hemisphere. *Advances in Neurology*, **7**, 147–183.

LENTNER C (1982) *Geigy Scientific Tables*, Volume 2, Eighth edition. Basle: Ciba-Geigy, pp. 222–224.

LUZZATTI C, SCOTTI G, GATTONI A (1979) Further suggestions for cerebral CT-localization. *Cortex*, **15**, 483–490.

MCCULLOUGH DC, HUANG HK, DEMICHELLE D, MANZ HJ (1979) Correlation between volumetric CT imaging and autopsy measurements of glioblastoma size. *Computerized Tomography*, **3**, 133–141.

MAZZOCCHI F, VIGNOLO LA (1978) Computer assisted tomography in neuropsychological research: a simple procedure for lesion mapping. *Cortex*, **14**, 136–144.

MILLER E (1970) Simple and choice reaction time following severe head injury. *Cortex*, **6**, 121–127.

NEWCOMBE F, RATCLIFF G (1989) Disorders of visuospatial analysis. In: *Handbook of Neuropsychology*, Volume 2. Edited by F. Boller and J. Grafmann. Amsterdam: Elsevier, pp. 333–356.

NORUŠIS MJ (1986) *SPSS/PC+ Advanced Statistics: For the IBM PC/XT/AT*. Chicago: SPSS.

RIEGE WH, KLANE LT, METTER EJ, HANSON WR (1982) Decision speed and bias after unilateral stroke. *Cortex*, **18**, 345–355.

TAKALA M (1951) Asymmetries of the visual space. *Annales Academiae Scientiarum Fennicae*, **B72**, 1–175.

TARTAGLIONE A, BENTON AL, RAITERI U, SENEGHINI A, COCITO L, FAVALE E (1981) Visual localization of points in a plane. *Journal of General Psychology*, **104**, 133–143.

TARTAGLIONE A, COCITO L, BINO G, PIZIO N, FAVALE E (1983) Further evidence for asymmetry of point localization in normals and unilateral brain damaged patients. *Neuropsychologia*, **21**, 407–412.

TARTAGLIONE A, BINO G, MANZINO M, SPADAVECCHIA L, FAVALE E (1986) Simple reaction-time changes in patients with unilateral brain damage. *Neuropsychologia*, **24**, 649–658.

TARTAGLIONE A, ONETO A, MANZINO M, FAVALE E (1987) Further evidence for focal effect of right hemisphere damage on simple reaction time. *Cortex*, **23**, 285–292.

TAYLOR MM (1961) Effect of anchoring and distance perception on the reproduction of forms. *Perceptual and Motor Skills*, **12**, 203–230.

VALLAR G, BISIACH E, STERZI R (1984) Hemispheric lateralization of the decisional stage in choice reaction times. A rejoinder to Heister and Schroeder-Heister. *Cortex*, **20**, 277–279.

VALLAR G, BISIACH E, CERIZZA M, RUSCONI ML (1988) The role of the left hemisphere in decision-making. *Cortex*, **24**, 399–410.

VAN ZOMEREN AH (1981) *Reaction Time and Attention after Closed Head Injury*. Lisse: Swets and Zeitlinger, pp. 1–161.

VAN ZOMEREN AH, DEELMAN BG (1976) Differential effects of simple and choice reaction after closed head injury. *Clinical Neurology and Neurosurgery*, **79**, 81–90.

VAN ZOMEREN AH, DEELMAN BG (1978) Long-term recovery of visual reaction time after closed head injury. *Journal of Neurology, Neurosurgery and Psychiatry*, **41**, 452–457.

VARNEY NR, BENTON AL (1975) Tactile perception of direction in relation to handedness and familial handedness. *Neuropsychologia*, **13**, 449–454.

VAUGHAN HG, COSTA LD (1962) Performance of patients with lateralized cerebral lesions. II: Sensory and motor tests. *Journal of Nervous and Mental Disease*, **134**, 237–243.

WINER BJ (1971) *Statistical Principles in Experimental Design*. Second edition. New York: McGraw-Hill.

WYKE M (1971) The effects of brain lesions on the performance of bilateral arm movements. *Neuropsychologia*, **9**, 33–42.

ZAIDEL E, ZAIDEL DW, SPERRY RW (1981) Left and right intelligence: case studies of Raven's Progressive Matrices following brain bisection and hemidecortication. *Cortex*, **17**, 167–185.

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LANGUAGE FUNCTIONS IN PROGRESSIVE SUPRANUCLEAR PALSY

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SUMMARY

Language functions were studied in 6 patients with clinically diagnosed progressive supranuclear palsy who conformed to the characteristic pattern of 'subcortical dementia'. Dysarthria, reading difficulties and disturbances of handwriting were present in all patients. Some patients showed additional deficits including visual dyslexia, constructional dysgraphia and an increased rate of self-corrections and misnamings in object confrontation naming. In most instances, the naming errors referred to an object visually similar to the target object, suggesting that visual misperception is the major cause of the naming disorder. It is concluded that a variety of language impairments may develop secondary to other neurological and neuropsychological changes in progressive supranuclear palsy.

INTRODUCTION

Progressive supranuclear palsy has been described by Steele *et al.* (1964) as a progressive brain disease of unknown aetiology with the clinical features of gaze palsy (primarily vertical), pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper trunk, dementia, and variable pyramidal and cerebellar signs. Neuropathologically, neuronal cell loss, gliosis, and neurofibrillary tangles are present in the brainstem, basal ganglia, and cerebellar nuclei (Steele *et al.*, 1964). Albert *et al.* (1974) described the dementia of supranuclear palsy as a type of 'subcortical dementia', characterized by a common pattern of forgetfulness, slowing of thought processes, emotional or personality changes (apathy or depression with occasional outbursts of irritability), and impaired ability to manipulate acquired knowledge. An absence of aphasia (as well as apraxia and agnosia) has been stressed as a conspicuous feature of subcortical dementia (Albert, 1978). Standardized psychometric tests focusing on specific language functions have, however, only recently been applied in patients with progressive supranuclear palsy (Maher *et al.*, 1985). In the present study, we present a comprehensive examination of language functions in 6 patients with progressive supranuclear palsy. Preliminary results of the study have already been published (Podoll *et al.*, 1988*b*).

PATIENTS AND SUBJECTS

Patients

Six patients with probable progressive supranuclear palsy who had been admitted to hospital between March 1986 and March 1988 were investigated. The diagnosis was made on the basis of the neurological examination and the history. In 1 patient (Case 5) pathological confirmation of the diagnosis subsequently

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became available. The clinical data are summarized in Table 1. All patients were male, right-handed and native German speakers. Their age ranged between 59 and 76 (mean 66.7) yrs. The time since onset of neurological symptoms ranged from 2 to 6 yrs, with a mean duration of 3.8 yrs prior to present admission. The Hoehn and Yahr (1967) staging scale was used to assess the degree of disability. Cranial CT scans revealed evidence of cerebral atrophy and ventricular dilatation in 5 of the 6 patients. Five of the 6 patients received neurotropic medication at the time of examination (levodopa and decarboxylase inhibitor preparation in 4 patients, bromocriptine in 2 patients and selegiline in 1 patient).

TABLE 1. PATIENTS' CLINICAL DATA

Case	*Age (yrs)*	*Sex*	*Disease duration (yrs)*	*Degree of disability**	*CT*	*MWT-B IQ*	*WAIS*		
							Verbal IQ	*Performance IQ*	*Full scale IQ*
1	73	M	2	III	Normal	118	95	80	87
2	59	M	3	III	Mild atrophy	94	73	57	63
3	61	M	3	IV	Severe atrophy	104	89	68	78
4	76	M	6	IV	Severe atrophy	112	98	68	82
5	63	M	5	V	Moderate to severe atrophy	101	91	64	77
6	68	M	4	V	Severe atrophy	ND	90	56	72

* Staging according to Hoehn and Yahr (1967). ND = not done.

Case 1. A 73-yr-old former manual worker developed dysarthria, dysphagia and progressive slowness, with frequent backward falls, at the age of 71 yrs. On clinical examination he showed a complete supranuclear ophthalmoplegia, saccadic pursuit movements and impaired suppression of the vestibulo-ocular reflex by fixation, pseudobulbar palsy with dysarthria and outbursts of forced laughter, a mild rigidity of the upper extremities, bradykinesia, retropulsion, and a slight sensorimotor polyneuropathy. The EEG and CT and MRI scans were normal.

Case 2. A former manual worker aged 59 yrs developed progressive slowness of movement, poor balance with backward falls, slurred speech, apathy and forgetfulness at the age of 56 yrs. On examination he had a complete vertical gaze palsy, horizontal gaze nystagmus and saccadic pursuit movements, dysarthria, mild rigidity of the neck and the upper extremities, bradykinesia, a resting tremor of both hands, and dementia. CT and MRI scans revealed mild cortical atrophy.

Case 3. A former locksmith aged 61 yrs developed, at the age of 58 yrs, progressive slowness of movement, poor balance with occasional falls, loss of dexterity for fine finger movements and slurred speech. Clinical examination demonstrated a complete vertical gaze palsy, pseudobulbar palsy with dysarthria and bilaterally pathological palmar-mental reflexes, marked hypokinesia, a predominantly right-sided spastic tetraparesis with pathologically exaggerated tendon reflexes, a slight intention tremor of the right hand, and dementia with marked mental slowing and forgetfulness. A CT scan revealed, in addition to severe cortical atrophy and expansion of the ventricles, a discrete hypodense lesion located in the left parietal and the left basal ganglia region (presumably an old ischaemic lesion).

Case 4. An engineer aged 76 yrs started to complain at the age of 70 yrs of progressive slowness of movement, poor balance with frequent backward falls, and slurred speech. On examination he showed complete vertical gaze palsy, horizontal gaze nystagmus and saccadic pursuit movements, dysarthria, marked nuchal rigidity and less pronounced rigidity of the extremities, bradykinesia with slowing of gait and bradydiadochokinesia, a slight tendency to retropulsion, a fluctuating slight resting tremor of the hands, and general mental slowing. A CT scan revealed a severe cerebral atrophy with enlargement of the ventricles.

Case 5. A retired policeman aged 63 yrs had a 5 yr history of walking difficulty, progressive forgetfulness, slurred speech and marked reading difficulties. On examination he was found to have an almost complete vertical gaze palsy, multiple-step hypometric saccades, saccadic pursuit movements, horizontal gaze nystagmus and impaired suppression of the vestibulo-ocular reflex by fixation, severe dysarthria, slight nuchal rigidity, bradykinesia, bilateral pathologically exaggerated upper limb tendon reflexes and a right extensor plantar response, slight sensory polyneuropathy, and marked mental slowing. A CT scan showed a moderate to severe cortical atrophy and enlargement of the ventricles. The patient died 11 mos after examination. The clinical diagnosis of progressive supranuclear palsy was confirmed at postmortem.

Case 6. A former locksmith aged 68 yrs started, at the age of 64 yrs, to experience progressive slowness of movement, frequent falls (most often backwards), forgetfulness and emotional lability with inappropriate outbursts of crying. Clinical examination revealed a nearly complete vertical gaze palsy, multiple-step hypometric saccades, saccadic pursuit movements, horizontal gaze nystagmus and impaired suppression of the vestibulo-ocular reflex by fixation, pseudobulbar palsy with dysarthria and pathological facial reflexes (snout reflex and palmar-mental reflexes), mild neck and less pronounced limb rigidity, bradykinesia, and a wide-based small-step ataxic gait with tendency to propulsion and retropulsion. There was evidence of dementia and marked visuoperceptual impairment. A CT scan demonstrated marked cortical atrophy and ventricular dilatation.

Control group

Ten healthy male volunteers without clinical evidence or history of CNS disorder were examined as a control group. The control group was matched to the patient group with respect to sex, age and duration of formal education. Their age ranged between 56 and 78 (mean 66.1) yrs.

Informed consent was obtained from the patients and their spouses and from the healthy volunteers.

METHODS

In addition to neurological and neuropsychological clinical examination, all patients and subjects were examined with the following psychometric tests.

The *multiple choice vocabulary test* (MWT-B, Lehrl, 1977) has been shown to be a reliable indicator of the premorbid level of verbal intelligence (Merz *et al.*, 1975). The test requires recognition of 1 correct word out of groups of 5 words which always contain 4 nonsense words and comprises 37 of these word groups.

The German version (HAWIE) of the *Wechsler Adult Intelligence Scale* (Wechsler, 1964) was applied with all subtests except the Vocabulary subtest.

The *Aachen Aphasia Test (AAT)* was used as a standardized neurolinguistically conceived psychometric aphasia test (Huber *et al.*, 1984).

All data analysis was carried out using nonparametric tests: the Mann-Whitney U test (Mann and Whitney, 1947) for between-group comparisons and the Wilcoxon matched-pairs signed-ranks test (Wilcoxon, 1945) for intra-group comparisons. Spearman's rank correlation coefficient r_s (with correction for ties; *see* Horn, 1942) was calculated as nonparametric correlational measure

RESULTS

Neuropsychological examination

All 6 patients complained of a general slowing of thinking, forgetfulness and lack of initiative. None of them reported episodes of major depression or outbursts of irritability. On clinical examination, there was no evidence of aphasic, agnostic or apraxic disturbances.

Drawing performance was examined by requiring the patients to draw a house and to copy a line drawing of a house (Moore and Wyke, 1984). The spontaneous drawings of 4 patients were unremarkable except for slight inaccuracies in the exact positioning of adjacent lines encountered in all drawings and the small size of two of the drawings (Cases 1 and 2). In 2 patients (Cases 5 and 6), the positioning of successively drawn adjacent lines was grossly distorted, giving the drawing a scattered and fragmented appearance and leading to an incorrect positioning of details in the drawing (fig. 1, left side). In both of these cases there was also gross impoverishment of the drawing,

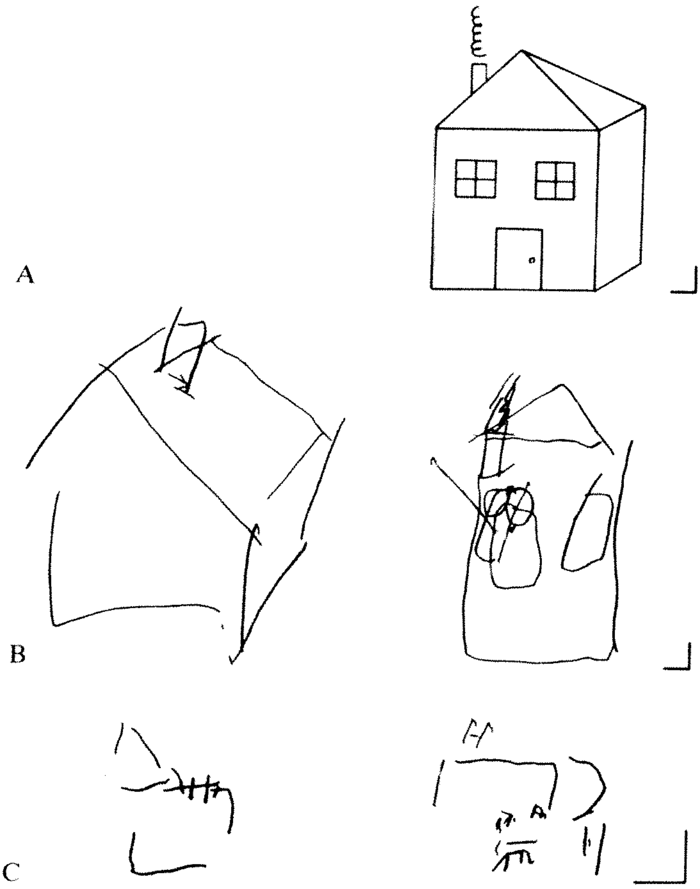

FIG. 1. Spontaneous drawings (*left*) and copies (*right*) of a drawing of a house (A) by 2 patients with progressive supranuclear palsy aged 63 yrs (B, *Case 5*) and 68 yrs (C, *Case 6*), respectively. Calibration bars represent 1 cm.

with essential features omitted (e.g., door, windows, roof). The copies showed essentially the same features as the spontaneous drawings, being normal in 4 patients and characterized by impoverishment of content and gross spatial distortion in the 2 patients (Cases 5 and 6) mentioned above (fig. 1, right side).

Intelligence testing

The mean MWT-B, verbal, performance and full scale WAIS IQ scores of the patients and the control subjects are given in Table 2.

The MWT-B could not be administered to 1 patient (Case 6) due to marked visual dyslexia; in the remaining 5 patients the MWT-B yielded an estimate of the premorbid IQ (Table 1) that was compatible with the level of formal education and professional occupation (*see* case histories). The mean MWT-B did not differ between the groups

TABLE 2 MEAN MWT-B AND WAIS SCORES

Test	*Controls* Mean ± SD	*Controls* n	*Patients* Mean ± SD	*Patients* n	*Comparison*
MWT-B score (IQ equivalent)	104.7±6.1	10	105.8±8.4	5	n.s.
WAIS					
Verbal IQ	106.4±6.1	10	89.3±7.9	6	$P < 0.005$
Performance IQ	101.0±10.5	10	65.5±8.0	6	$P < 0.005$
Full Scale IQ	104.0±7.8	10	76.5±7.6	6	$P < 0.005$
WAIS subtest score					
Information	10.2±1.2	10	8.8±2.0	6	n.s.
Comprehension	11.2±1.9	10	7.3±2.4	6	$P < 0.01$
Digit Span	9.4±1.6	10	7.3±2.1	6	$P < 0.05$
Arithmetic	8.7±1.6	10	5.2±2.0	6	$P < 0.005$
Similarities	10.1±1.9	10	5.5±2.9	6	$P < 0.005$
Digit Symbol	7.7±3.0	10	1.3±1.4	6	$P < 0.005$
Picture Arrangement	9.0±2.7	10	3.7±1.9	6	$P < 0.005$
Picture Completion	9.3±2.1	10	3.3±2.8	6	$P < 0.005$
Block Design	6.9±2.1	10	2.2±0.9	6	$P < 0.005$
Object Assembly	9.9±1.4	10	1.7±2.1	6	$P < 0.001$

of the patients and the control subjects, indicating that the control group was matched to the premorbid intelligence level of the patient group.

On WAIS testing, the mean verbal, performance and full scales IQ were significantly reduced in the patient group (Table 2).

In the patient group, there was a significant difference ($P < 0.05$) between the MWT-B and verbal IQ scores, the MWT-B and performance IQ scores, the MWT-B and full scale IQ scores and the verbal and performance IQ scores.

The discrepancy between the MWT-B IQ, which can be used as an estimate of the premorbid IQ, and the full scale WAIS IQ was recorded as an index of deterioration. In the control group, the mean (±SD) discrepancy was 0.7±2.8 ($n = 10$) with a range of −5 to 4. In the patient group, the mean (±SD) discrepancy was 28.4±2.9 ($n = 5$) with a range of 24−31.

Comparisons of the results of neuropsychological testing with findings of the CT scans did not reveal any correlation between the severity of intellectual impairment and the degree of cerebral atrophy.

Examination of language functions

Results of examination with the AAT are summarized in Table 3.

Spontaneous speech

Communicative disability resulted primarily from the general mental slowing and from dysarthria which was found in all the patients. Two patients displayed a mild dysarthria, resulting in some loss of fluency of speech, and 4 patients showed a severe dysarthria, rendering some of their speech utterances only partially intelligible. Some phonemic uncertaincies were present in all patients as a consequence of their dysarthria (according to the AAT criteria, these were not considered in the AAT ratings of phonemic structure).

TABLE 3. AAT SCORES (MEAN ± SD AND RANGE)

Subtest/parts	*Controls (n = 10)*	*Patients (n = 6)*	*Comparison*
Spontaneous speech			
Verbal communication	5.0±0.0	2.3±0.9 (1–4)	$P < 0.005$
Articulation and prosody	5.0±0.0	2.3±0.5 (2–3)	$P < 0.005$
Automatic speech elements	5.0±0.0	5.0±0.0	n.s.
Semantic structure	5.0±0.0	5.0±0.0	n.s.
Phonemic structure	5.0±0.0	5.0±0.0	n.s.
Syntactic structure*	5.0±0.0		
Token Test	0.3±0.6 (0–2)	2.8±2.0 (0–6)	$P < 0.01$
Repetition	147.2±1.2 (145–149)	139.8±7.4 (125–148)	$P < 0.05$
Single phonemes	29.7±0.5 (29–30)	27.0±1.3 (25–29)	$P < 0.005$
One syllable words	29.5±0.9 (27–30)	27.8±1.8 (25–30)	$P < 0.05$
Loan and foreign words	29.8±0.4 (29–30)	28.7±1.6 (26–30)	n.s.
Compound nouns	29.0±0.9 (28–30)	28.5±1.5 (26–30)	n.s.
Sentences	29.2±0.7 (28–30)	27.8±3.1 (21–30)	n.s.
Written language	88.2±1.2 (86–90)	64.7±20.1 (27–84)	$P < 0.005$
Reading aloud	29.6±0.5 (29–30)	24.0±5.3 (14–29)	$P < 0.005$
Selecting/combining	29.7±0.5 (29–30)	19.3±13.7 (0–30)	$P < 0.005$
Writing to dictation	28.9±0.8 (28–30)	21.3±4.8 (13–27)	$P < 0.005$
Naming on confrontation	113.4±2.1 (109–116)	94.3±11.2 (74–107)	$P < 0.005$
Objects (simple nouns)	29.2±0.9 (28–30)	25.2±4.6 (17–30)	$P < 0.005$
Colours	29.6±0.8 (28–30)	25.0±3.1 (19–29)	$P < 0.005$
Objects (compound nouns)	29.4±0.5 (29–30)	25.3±3.0 (21–30)	$P < 0.05$
Situations	25.2±1.7 (23–28)	18.8±4.0 (11–23)	$P < 0.005$
Comprehension	110.5±5.4 (101–119)	83.0±17.6 (61–101)	$P < 0.005$
Auditory comprehension of words	27.2±2.2 (22–30)	23.3±4.3 (14–27)	$P < 0.05$
Auditory comprehension of sentences	26.5±3.3 (21–30)	17.8±5.0 (10–24)	$P < 0.01$
Reading comprehension of words	28.4±1.1 (26–30)	21.8±5.7 (13–28)	$P < 0.005$
Reading comprehension of sentences	28.4±1.7 (25–30)	20.0±6.8 (11–30)	$P < 0.05$

* Syntax of patients with progressive supranuclear palsy could not be classified according to AAT scoring criteria.

The semantic structure of spontaneous speech was unremarkable, and there was no evidence of word-finding difficulty, as indicated by word-finding pauses, circumlocutions or semantic paraphasia. Syntactic structure was normal in 2 patients, and characterized by short simple sentence constructions, with a tendency to leave sentences unfinished in the other 4 patients (a finding which did not fulfil any of the AAT rating criteria for syntax, so that no AAT ratings are provided in Table 3 for this level of observation). There was no evidence for agrammatism. There were no automatic speech elements in the patients' spontaneous speech. During the interview, 1 patient (Case 1) occasionally emitted forced laughter.

Token Test

The performance in the Token Test was significantly impaired in the patient group (Table 3). While none of the control subjects made more than 2 errors, this error number was exceeded by 2 of the patients (Cases 2 and 3) who had a total score of 5 and 6, respectively.

Repetition

Except for the uncertaincies of articulation due to the dysarthria, repetition performance was normal in all 6 patients.

Written language

Reading aloud. Subjects were asked to read aloud 10 verbal stimuli: 7 words and 3 sentences, printed in capital letters of 1 cm height on separate cards. Reading performance was normal in the control subjects. Reading was slowed and pronunciation was affected by dysarthria in all 6 patients. In addition, 3 patients (Cases 4, 5, 6) showed a lack of fluency in reading, deciphering words in a hesitant, disconnected manner, with pauses inserted after spelling out a single letter or syllable and with multiple self-corrections. Two patients (Cases 5, 6) showed reading errors indicative of visual dyslexia, producing lexically existent words that were related to the stimulus by orthographic (visual) similarity, e.g.,

Stimulus	*Response*
Quirl	Qual
schlicht	Schicht schlecht
Sportler	Sportlehrer
Eitelkeit	Ehrlichkeit

One of these patients (Case 6), who showed visual dyslexia in response to 6 of the 10 items, displayed a number of other reading errors in response to the other items, including the substitution and addition of a letter and the omission of a word.

Combination of letters and words. Subjects were asked to combine letters into words or words into sentences from a set of 16 letters or 16 words, respectively, printed on white cards arranged in a standardized stimulus array. Two patients (Cases 5, 6) were unable to match the 16 stimulus cards to the corresponding positions of the stimulus array (probably due to visual scanning deficits), so that the subtest could not be performed.

The performance of the other 4 patients was similar to that of the control group and showed only minor errors (1 patient omitted letters in 2 words, 1 patient omitted a word in the reproduction of a stimulus sentence, 1 patient required the repetition of 1 stimulus word).

Writing to dictation. Ten verbal stimuli, 7 words and 3 sentences, were dictated to the subjects. Writing to dictation was normal in the control group. In all 6 patients, writing was executed laboriously and with reduced speed. Due to the loss of dexterity in fine finger movements, graphical performance was impaired and legibility of the script was degraded to varying degrees in all 6 patients. Three patients (Cases 3, 5, 6) showed a considerable slanting of the line away from the horizontal. Script size was normal in 3 patients. One patient (Case 2) showed a tendency to micrographia and 1 patient (Case 6) a marked micrographia, resulting in the virtual illegibility of his script. Another patient (Case 5) displayed macrographia with an average height of letters between 1.5 and 2.0 cm. This latter patient complained that he could not see his script while he was writing; he explained that he could write 'only out of memory'.

An error analysis of the writing specimens revealed that, in addition to the obvious degradation of graphical performance, particular kinds of dysgraphic errors occurred in 4 patients (Cases 2, 4, 5, 6). The total of 19 dysgraphic responses observed in the patient group comprised 79% omissions of letters, the most frequent error type, 21% omissions of a word within a sentence, 1 perseveration of a letter or of a word, and 1 substitution of a letter (since a dysgraphic response could comprise multiple errors, percentages do not add up to 100%).

As additional tests, the test items of the AAT were printed in capital letters of 1 cm height and the subjects were asked first to transcribe and then to copy the words and sentences. In the control group, both tasks were performed without errors. In the transcriptions made by the patients, a total of 15 dysgraphic responses consisted of 87% omissions of letters, 1 omission of a word, 1 perseveration and 1 addition of a letter, and 1 error with a reversal of the order of 2 adjacent letters. The patient (Case 6) with severe visual dyslexia produced—in his virtually illegible micrographic script—almost exclusively corresponding errors of transcription. The task of producing an exact copy of the printed test stimuli to be placed below the model imposed additional difficulties for the patients. A total of 12 dysgraphic responses included 92% omissions of letters, 1 omission of a word, 33% perseverations of letters, and 1 error with a reversal of the sequential order of successive letters. Fig. 2 shows that the perseverative errors encountered in this patient (Case 4) appeared to be related to difficulties in gaze shifting from model to copy and vice versa. One patient (Case 5) followed a strategy that circumvented the demands of the copy task and placed a transcription using block letters below the model. The same strategy was used by the patient (Case 6) with severe visual dyslexia who also produced corresponding errors in the copying task. One patient (Case 2) was able to copy words but refused to complete the test when required to copy sentences.

Naming

Object confrontation naming. Parts 1 and 3 of the AAT subtest Naming, each consisting of 10 outline drawings of objects corresponding to 10 simple nouns and 10 compound nouns, respectively, were combined for an assessment of object confrontation naming.

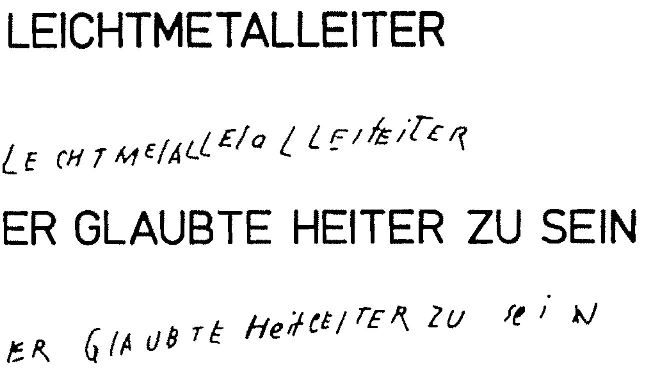
LEICHTMETALLEITER
LE CHTMEIALLEla L LEIteiTER
ER GLAUBTE HEITER ZU SEIN
ER GlAUBTE HeitteiTER ZU SEI N

FIG. 2. Copy writing of a 76-yr-old patient with progressive supranuclear palsy (*Case 2*). The copies show multiple perseverations which arise from difficulties in gaze shifting between model and copy and vice versa.

The mean naming error rate, calculated by dividing the total number of errors by the total number of items, was 2.5% in the control group and 15.0% in the patients. Analysis with the Mann-Whitney U test found this group difference to be statistically significant ($U = 6.0$, $z = -2.72$, $P < 0.01$). Considering individual test performances, a maximum of 2 naming errors was observed in the control subjects. Four of the 6 patients also gave no more than 2 incorrect responses, while 2 patients (Cases 3, 6) exceeded the normal range of variability and made 5 and 7 errors, respectively.

Naming errors were categorized according to error type. Of the total of 18 errors made by the group of patients, 16 or 89% were classified as related to the target item: 67% (12/18) of the total naming errors were purely visually related but in no other way similar to the target item, 17% (3/18) were both visually and semantically related naming errors, and 6% (1/18) purely semantically associated naming errors. In 11% (2/18) of the total naming errors, no naming response was provided; in both cases the patient indicated that he did not recognize the depicted object. Naming errors that were unrelated to the target item were not observed.

Spontaneous self-corrections of false responses occurred in 1.0% of the trials in the control group and with a significantly higher frequency of 7.0% in the patient group ($U = 14.0$, $z = -2.02$, $P < 0.05$). Whereas up to 1 self-correction was encountered in the control group, this number was exceeded by 2 patients (Cases 3, 6) who made 3 self-corrections each. Of the total of 8 initial misnamings that were spontaneously corrected by the patients, 63% (5/8) were both visually and semantically related to the target item, 25% (2/8) were purely visually associated and 13% (1/8) purely semantically associated. Of the 6 misnamings that showed a semantic relation, 50% (3/6) indicated objects of the same category, 33% (2/6) were superordinates and 17% (1/6) represented a circumlocution indicating the function of the target object.

In the trials with correct naming responses, naming latencies were similar for the control subjects and the patients and in no instance exceeded 10 s in either group.

Colour naming. In part 2 of the AAT subtest Naming, the subjects were confronted with 10 squares of different colours. The mean error rate in colour naming was 1.0% in the control group and 12.5% in the patient group ($U = 5.5$, $z = -3.06$, $P < 0.005$). In a single instance no naming response was provided at all, while the other errors lay in the application of an incorrect colour term. In all 6 patients, a normal performance on Ishihara's pseudoisochromatic plates (Ishihara, 1972) was documented on ophthalmologic examinations before the onset of the illness, which argues against colour blindness as the cause of the increased error rate in colour naming.

Picture description. In part 4 of the AAT Naming subtest, 10 pictures of everyday events were presented which must be described in one sentence. With respect to propositional contents, patients with progressive supranuclear palsy had an impairment in picture description that reflected primarily an inability to convey the information presented in the stimulus pictures. With respect to the syntactic structure, there was no evidence of agrammatism in the sentence production.

Comprehension

The AAT subtest Comprehension consists of two types of multiple-choice word-picture and sentence-picture tasks, the verbal stimuli being presented aurally or visually. Only 1 patient was able to perform within the normal range of variability in the Comprehension subtest. There was a high correlation between the impairment in the Comprehension subtest and the Wechsler full scale IQ (Spearman's rank correlation coefficient $r_S = +0.77$). In the patient group, comprehension of words was found to be superior to comprehension of sentences. In 4 patients there was no marked difference between auditory and reading comprehension, 1 patient (Case 1) demonstrated a slightly superior reading comprehension, and the patient (Case 6) who showed a severe visual dyslexia had consequent impairment of reading comprehension.

DISCUSSION

Intellectual impairment in progressive supranuclear palsy

In the 6 patients with progressive supranuclear palsy investigated in the present study, clinical neuropsychological examination revealed a pattern of intellectual impairment that has been characterized as 'subcortical dementia' by Albert *et al.* (1974). Intellectual impairment could be confirmed in all of the patients studied by a standardized psychometric examination with the German version of the WAIS. Although most of the reports of neuropsychological assessment in patients with progressive supranuclear palsy have shown evidence of some intellectual impairment (Messert and van Nuis, 1966; David *et al.*, 1968; Dix *et al.*, 1970; Parkes *et al.*, 1971; Jackson *et al.*, 1983; Maher *et al.*, 1985), it has been questioned whether this evidence from psychometric testing reflects a genuine intellectual decline or whether impaired performance on neuropsychological tests results from visual searching or scanning difficulties, as suggested by Kimura *et al.* (1981) and Fisk *et al.* (1982). In the present study, both verbal and performance IQ scores were impaired when compared with a control group matched for age, sex, and premorbid level of intelligence (as estimated by the performance in the multiple choice vocabulary test, MWT-B). Moreover, in the patients with progressive supranuclear palsy both verbal and performance IQ scores were significantly reduced when compared with the premorbid IQ. This impairment of the verbal IQ cannot be explained by visual difficulties. These psychometric test results confirm the results obtained in a larger sample of 33 patients reported by Maher *et al.* (1985) who found significant differences between the premorbid IQ (as assessed by the performance in the National Adult Reading Test, cf. Nelson, 1982) and the WAIS verbal and performance IQ scores in patients with progressive supranuclear palsy.

Communicative disability

The communicative disability of patients with supranuclear palsy primarily results from the dysarthria that was present in different degrees in all of the 6 patients studied in the present series. In the clinical course of the disease, dysarthria may occur as the earliest symptom and may eventually progress to complete anarthria (Steele, 1972; Probst and Dufresne, 1975). Dysarthric speech in progressive supranuclear palsy is characterized by a slow rate, low volume, and monotonous prosody. Palilalia has been frequently observed (Alajouanine *et al.*, 1928; Kissel *et al.*, 1967; David *et al.*, 1968; Behrman *et al.*, 1969; De Renzi and Vignolo, 1969; Constantinidis *et al.*, 1970; Colmant, 1971; Mastaglia *et al.*, 1973; Rouzaud *et al.*, 1974; Rafal and Grimm, 1981), but was not found in the present series. Forced laughter (Messert and van Nuis, 1966; Anastasopoulos *et al.*, 1967; David *et al.*, 1968; Dix *et al.*, 1971; Janati and Appel, 1984; Heckl, 1985) or inappropriate outbursts of crying (Alajouanine *et al.*, 1928; Anastasopoulos *et al.*, 1967; David *et al.*, 1968; Albert *et al.*, 1974; Ishino *et al.*, 1974; Janati and Appel, 1984; Heckl, 1985) occur in many patients, but less commonly than with other forms of pseudobulbar paralysis (Steele, 1972). Hanson and Metter (1980) used a delayed auditory feedback device as instrumental treatment for dysarthria in a patient with progressive supranuclear palsy.

While garrulity and a tendency for loquacity (Messert and van Nuis, 1966) and irrelevant rambling (David *et al.*, 1968) has been described in some patients at the beginning of the disease when dysarthria is still mild, most patients show a typical muteness in the further course of the disease (Constantinidis *et al.*, 1970; Albert *et al.*, 1974; Janati and Appel, 1984). The patient does not speak spontaneously (Dix *et al.*, 1971), but may continue to answer simple questions (David *et al.*, 1968; Rouzaud *et al.*, 1974). In conversation, the latencies between questions and the patients' responses may be inordinately long (Albert *et al.*, 1974; Rouzaud *et al.*, 1974; Davis *et al.*, 1985), sometimes taxing the patience of the examiner (Albert *et al.*, 1974). In occasional observations, patients who were rendered totally mute by anarthria developed alternative communicative strategies and used writing (Anastasopoulos *et al.*, 1967) or made reasonable appropriate responses to simple questions through eye blinks or slow gross movements of the extremities (David *et al.*, 1968).

Written language

Reading difficulties are mentioned in many case reports of patients with progressive supranuclear palsy (David *et al.*, 1968; Dix *et al.*, 1971; Klawans and Ringel, 1971). Pfaffenbach *et al.* (1972) reported complaints of difficulties in reading in 43% of a sample of 44 patients with progressive supranuclear palsy. However, formal analysis of reading errors has not yet been reported.

In the present study, reading performance was affected by dysarthric speech impairment in all 6 patients. In addition to this dysarthric impairment, 3 patients had reading difficulties that appeared to be due to a disturbance in visual registration during reading (Marshall and Newcombe, 1973) that could be related to the well-documented oculomotor disorders in progressive supranuclear palsy (Newman *et al.*, 1970; Dix *et al.*, 1971; Pfaffenbach *et al.*, 1972; Troost and Daroff, 1977; Pierrot-Deseilligny *et al.*, 1989). They deciphered words in a hesitant, disconnected manner. Similarly, a patient studied by Constantinidis *et al.* (1970) promptly recognized single letters or syllables presented in the visual axis of his gaze, but had marked difficulties when asked to read a long word or a phrase, grasping clues only, skipping over words and jumping from one line to another. Two patients participating in the present study produced a type of reading error indicative of visual dyslexia (Marshall and Newcombe, 1973), the reading errors representing a valid word with visual (i.e., orthographic) similarity to the stimulus word. Visual dyslexia has also been described in some patients with Huntington's disease, another major representative of basal ganglia disorder (Podoll *et al.*, 1988*a*).

In handwriting, a deterioration of graphic performance could be observed in all 6 patients in the present study. The script of patients with progressive supranuclear palsy has been reported to become cramped (Alajouanine *et al.*, 1928; Steele *et al.*, 1964) and, finally, illegible (Alajouanine *et al.*, 1928; Steele *et al.*, 1964; Kissel *et al.*, 1967; David *et al.*, 1968; Probst and Dufresne, 1975; Heckl, 1985). In the handwriting of a patient studied by Alajouanine *et al.* (1928), letters were transformed into strokes of high similarity which lead to a peculiar uniformity of characters with resulting illegibility of the script. In some patients, handwriting showed the typical extrapyramidal feature of micrographia (Albert *et al.*, 1964; Kissel *et al.*, 1967; Constantinidis *et al.*, 1970; Dix *et al.*, 1971; Rouzaud *et al.*, 1974; Probst and Dufresne, 1975). The patient of Constantinidis *et al.* (1970) showed marked visuospatial perturbations in his handwriting.

Dysgraphic errors—including omissions, perseverations and substitutions of letters or words— were encountered in 4 of the 6 patients studied in the present series. Similarly, Obler and Albert (1981) reported a patient who omitted and added letters in writing to dictation. The dysgraphic errors observed in patients with supranuclear palsy are probably due to an impairment of visual monitoring processes executed during writing. Pfaffenbach *et al.* (1972) remarked that the palsy of downward gaze makes writing troublesome for many patients. One patient examined in the present study explicitly stated that he could not see his script while he was writing. Experiments in normal subjects demonstrated that handwriting is a motor skill which suffers when visual feedback is altered (Smith *et al.*, 1960). The frequent occurrence of omissions and perseverations suggests that visual feedback is important in updating the graphic motor pattern as to which letters have already been executed.

The oculomotor disturbances in progressive supranuclear palsy also affect the graphic performance in the nonlinguistic tasks of drawing and copying. Thus the performance of 2 patients participating in this study was characterized by omissions of essential features, resulting in an impoverishment of the drawings, and gross spatial distortion. It is reasonable to assume that structurally similar errors in the acts of writing and drawing are both due to visuoconstructional disabilities, which allow the classification of the writing disturbance of progressive supranuclear palsy patients as a variety of constructional dysgraphia (*see* Leischner, 1969). This notion is also consistent with the observation that the 2 patients mentioned above were unable to combine letters into words from a set of printed letters.

Semantic structure of spontaneous speech

The absence of aphasic disturbance in the spontaneous speech of patients with progressive supranuclear palsy has been stressed by several investigators, as summarized by Albert *et al.* (1974). As exceptional observations, Perkin *et al.* (1978) presented

2 well-documented cases of mildly demented patients with marked dysphasia. In 2 neuropathologically confirmed cases (Kish *et al.*, 1985), the clinical notes made mention of a severe dysphasia (without further neurolinguistic characterization) and an aphasia with paraphasic word substitution, respectively. Maher *et al.* (1985) reported, in a retrospective study, mild word-finding difficulties without evidence of more severe dysphasia in 7 of 25 patients. However, the interpretation of these clinical observations is not unequivocal, since inappropriate silences may appear in the speech as a consequence of dysarthria that may mimic true word-finding difficulties, as has already been pointed out by Constantinidis *et al.* (1970). In the present study, no clinical evidence of word-finding difficulty was apparent during spontaneous speech, nor did the patients or their relatives report specific word-finding difficulties. Thus further work is needed to clarify whether the semantic structure of spontaneous speech is impaired in progressive supranuclear palsy.

Visual confrontation naming

In the few studies that have formally examined visual confrontation naming in patients with progressive supranuclear palsy (Constantinidis *et al.*, 1970; Albert *et al.*, 1974; Maher *et al.*, 1985), naming performance was found to be normal, except for the prolonged naming latencies displayed by 1 patient (Constantinidis *et al.*, 1970). In the present study, 2 of 6 patients displayed an increased rate of spontaneous self-corrections and an increased naming error rate. Categorization of the corpus of 18 naming errors collected in the total group of 6 patients according to error type revealed that visually-related naming errors accounted for 83% (15/18) of the naming errors, 67% (12/18) being purely visually-related and 17% (3/18) being both visually and semantically-related naming errors. In these instances, the misnamings referred to objects visually similar in appearance to the depicted object. Only 1 naming error was a purely semantically associated misnaming. This result suggests that the impairment in visual confrontation naming is due primarily to an impairment at the encoding stage of naming, where processes of visual perception are involved (*see* Caramazza and Berndt, 1978). A qualitative analysis of erroneous naming responses suggests that the visuoperceptive difficulties involve a neglect of visual features that are crucial for a correct identification of the object in the majority of the visually-related naming errors. The presence of disturbances of visual information processing in progressive supranuclear palsy has been demonstrated by a variety of neuropsychological tests (Kimura *et al.*, 1981; Maher *et al.*, 1985; Rafal *et al.*, 1988). The interpretation of the naming impairment in terms of a visual perceptual deficit also accounts for the contrast between the marked naming disorder encountered in 2 patients of the present study and the absence of word-finding difficulties in their spontaneous speech, since only in the first situation is a level of sensory stimulation involved where visual misperception can result in a disruption of naming.

Syntax

In the present study, syntactic structure of spontaneous speech was normal in 2 patients with mild dysarthria and characterized by a preponderance of short simple sentence constructions with a tendency to leave sentences unfinished in 4 patients exhibiting a severe dysarthria. Thus the preponderance of short simple sentence constructions appears primarily related to the development of dysarthria which places constraints on the patient's ability to maintain the flow of speech for longer periods, favouring the use of syntactic strategies associated with an economy of effort for speech output. No evidence of agrammatism was found in spontaneous speech or in the sentence production elicited by a picture description task in the 6 patients examined in the present study.

Conclusions

In the present study, language functions were studied in 6 patients with progressive supranuclear palsy who clinically and psychometrically conformed to the characteristic pattern of subcortical dementia as described by Albert *et al.* (1974). Whereas dysarthria, mild reading difficulties and disturbances of handwriting were apparent in all the patients studied, additional deficits in language behaviour secondary to visuoperceptive impairment were encountered in some patients, including visual dyslexia, constructional dysgraphia and an increased error rate in object confrontation naming. In accordance with the pattern of subcortical dementia, no evidence of primary aphasic disorders was found in the present study. The pattern of language impairments observed in the present series of patients with progressive supranuclear palsy is similar to that encountered in patients with Huntington's disease (Podoll *et al.*, 1988*a*), a basal ganglia disorder which has been designated as another major representative of subcortical dementia (McHugh and Folstein, 1975). In summary, whereas there appear to be no primary language changes in progressive supranuclear palsy, a variety of language impairments may develop secondary to other neurological and neuropsychological disturbances, namely parkinsonism, dysarthria, oculomotor disorder, visuoperceptive impairment and constructional disability.

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REFERENCES

ALAJOUANINE T, SCHIFF P, SCHIFF S, MONTASSUT M (1928) Dysgraphie hypertonique et syndrome de Parinaud chez un pseudo-bulbaire extrapyramidal. *Revue Neurologique*, **1**, 112–116.

ALBERT ML (1978) Subcortical dementia. In: *Alzheimer's Disease: Senile Dementia and Related Disorders.* Edited by R. Katzman, R. D. Terry and K. L. Bick. New York: Raven Press, pp. 173–180.

ALBERT ML, FELDMAN RG, WILLIS AL (1974) The 'subcortical dementia' of progressive supranuclear palsy. *Journal of Neurology, Neurosurgery and Psychiatry*, **37**, 121–130.

ANASTASOPOULOS G, ROUTSONIS C, CONSTAS CG (1967) Dystonie oculo-facio-cervicale (*progressive supranuclear palsy*). *Revue Neurologique*, **116**, 85–88.

BEHRMAN S, CARROLL JD, JANOTA I, MATTHEWS WB (1969) Progressive supranuclear palsy: clinicopathological study of four cases. *Brain*, **92**, 663–678.

CARAMAZZA A, BERNDT RS (1978) Semantic and syntactic processes in aphasia: a review of the literature. *Psychological Bulletin*, **85**, 898–918.

COLMANT HJ (1971) Progressive supranuclear palsy. *Archiv für Psychiatrie und Nervenkrankheiten*, **214**, 324–330.

Constantinidis J, Tissot R, Ajuriaguerra J de (1970) Dystonie oculo-facio-cervicale ou paralysie progressive supranucléaire de Steele-Richardson-Olszewski: pseudo-paralysie du regard, troubles visuo-spatiaux, pseudo-démence, altérations neuronales. *Revue Neurologique*, **122**, 249–262.

David NJ, Mackey EA, Smith JL (1968) Further observations in progressive supranuclear palsy. *Neurology, Minneapolis*, **18**, 349–356.

Davis PH, Bergeron C, McLachlan DR (1985) Atypical presentation of progressive supranuclear palsy. *Annals of Neurology*, **17**, 337–343.

De Renzi E, Vignolo LA (1969) L-dopa for progressive supranuclear palsy. *Lancet*, **ii**, 1360.

Dix MR, Harrison MJG, Lewis PD (1971) Progressive supranuclear palsy (the Steele-Richardson-Olszewski syndrome): a report of 9 cases with particular reference to the mechanism of the oculomotor disorder. *Journal of the Neurological Sciences*, **13**, 237–256.

Fisk JD, Goodale MA, Burkhart G, Barnett HJM (1982) Progressive supranuclear palsy: the relationship between ocular motor dysfunction and psychological test performance. *Neurology, New York*, **32**, 698–705.

Hanson WR, Metter EJ (1980) DAF as instrumental treatment for dysarthria in progressive supranuclear palsy: a case report. *Journal of Speech and Hearing Disorders*, **45**, 268–276.

Heckl RW (1985) Die progressive supranukleäre Ophthalmoplegie—Eine klinische Einheit? *Fortschritte der Neurologie und Psychiatrie*, **53**, 33–41.

Hoehn MM, Yahr MD (1967) Parkinsonism: onset, progression, and mortality. *Neurology, Minneapolis*, **17**, 427–442.

Horn D (1942) A correction for the effect of tied ranks on the value of the rank difference correlation coefficient. *Journal of Educational Psychology*, **33**, 686–690.

Huber W, Poeck K, Willmes K (1984) The Aachen Aphasia Test. *Advances in Neurology*, **42**, 291–303.

Ishihara S (1972) *Ishihara's Tests for Colour Blindness*. Tokyo: Shuppan.

Ishino H, Higashi H, Kuroda S, Yabuki S, Hayahara T, Otsuki S (1974) Motor nuclear involvement in progressive supranuclear palsy. *Journal of the Neurological Sciences*, **22**, 235–244.

Jackson JA, Jankovic J, Ford J (1983) Progressive supranuclear palsy: clinical features and response to treatment in 16 patients. *Annals of Neurology*, **13**, 273–278.

Janati A, Appel AR (1984) Psychiatric aspects of progressive supranuclear palsy. *Journal of Nervous and Mental Disease*, **172**, 85–89.

Kimura D, Barnett HJM, Burkhart G (1981) The psychological test pattern in progressive supranuclear palsy. *Neuropsychologia*, **19**, 301–306.

Kish SJ, Chang LJ, Mirchandani L, Shannak K, Hornykiewicz O (1985) Progressive supranuclear palsy: relationship between extrapyramidal disturbances, dementia, and brain neurotransmitter markers. *Annals of Neurology*, **18**, 530–536.

Kissel P, Cordier J, Picard L (1967) Dystonie oculo-facio-cervicale (syndrome de Steele, Richardson et Olszewski). *Revue d'Oto-Neuro-Ophtalmologie*, **39**, 113–118.

Klawans HL, Ringel SP (1971) Observations on the efficacy of L-dopa in progressive supranuclear palsy. *European Neurology*, **5**, 115–129.

Lehrl S (1977) *Manual zum MWT-B*. Erlangen: Straube.

Leischner A (1969) The agraphias. In: *Handbook of Clinical Neurology*, Volume 4. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, pp. 141–180.

McHugh PR, Folstein MF (1975) Psychiatric syndromes of Huntington's chorea: a clinical and phenomenologic study. In: *Psychiatric Aspects of Neurological Disease*. Edited by D. F. Benson and D. Blumer. New York and London: Grune and Stratton, pp. 267–285.

Maher ER, Smith EM, Lees AJ (1985) Cognitive deficits in the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Journal of Neurology, Neurosurgery and Psychiatry*, **48**, 1234–1239.

Mann HB, Whitney DR (1947) On a test of whether one of two random variables is stochastically larger than the other. *Annals of Mathematical Statistics*, **18**, 50–60.

Marshall JC, Newcombe F (1973) Patterns of paralexia: a psycholinguistic approach. *Journal of Psycholinguistic Research*, **2**, 175–199.

Mastaglia FL, Grainger K, Kee F, Sadka M, Lefroy R (1973) Progressive supranuclear palsy (the Steele-Richardson-Olszewski syndrome): clinical and electrophysiological observations in eleven cases. *Proceedings of the Australian Association of Neurologists*, **10**, 35–44.

MERZ JS, LEHRL S, ERZIGKEIT H, GALSTER JV (1975) MWT-B: ein Intelligenzkurztest. *Psychiatrie, Neurologie und Medizinische Psychologie, Leipzig*, **27**, 424–428.

MESSERT B, VAN NUIS C (1966) A syndrome of paralysis of downward gaze, dysarthria, pseudobulbar palsy, axial rigidity of neck and trunk and dementia. *Journal of Nervous and Mental Disease*, **143**, 47–54.

MOORE V, WYKE MA (1984) Drawing disability in patients with senile dementia. *Psychological Medicine*, **14**, 97–105.

NELSON HE (1982) *National Adult Reading Test*. Windsor, Berkshire: NFER-Nelson.

NEWMAN N, GAY AJ, STROUD MH, BROOKS J (1970) Defective rapid eye movements in progressive supranuclear palsy: an ocular electromyographic study. *Brain*, **93**, 775–784.

OBLER LK, ALBERT ML (1981) Language and aging: a neurobehavioral analysis. In: *Aging: Communication Processes and Disorders*. Edited by D. S. Beasley and G. A. Davis. New York and London: Grune and Stratton, pp. 107–121.

PARKES JD, KNILL-JONES RP, CLEMENTS PJ (1971) L-dopa and amantadine hydrochloride in extra-pyramidal disorders. *Postgraduate Medical Journal*, **47**, 116–119.

PERKIN GD, LEES AJ, STERN GM, KOCEN RS (1978) Problems in the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome). *Canadian Journal of Neurological Sciences*, **5**, 167–173.

PFAFFENBACH DD, LAYTON DD, KEARNS TP (1972) Ocular manifestations in progressive supranuclear palsy. *American Journal of Ophthalmology*, **74**, 1179–1184.

PIERROT-DESEILLIGNY CH, RIVAUD S, PILLON B, FOURNIER E, AGID Y (1989) Lateral visually-guided saccades in progressive supranuclear palsy. *Brain*, **112**, 471–487.

PODOLL K, CASPARY P, LANGE HW, NOTH J (1988*a*) Language functions in Huntington's disease. *Brain*, **111**, 1475–1503.

PODOLL K, SCHWARZ M, NOTH J (1988*b*) Sprachverhalten bei Patienten mit progressiver supranukleärer Blicklähmung (Steele-Richardson-Olszewski-Syndrom). *Psycho*, **14**, 388–389.

PROBST A, DUFRESNE JJ (1975) Paralysie supranucléaire progressive (ou dystonie oculo-facio-cervicale). Etude clinique et neuropathologique. *Archives Suisses de Neurologie, Neurochirurgie et de Psychiatrie*, **116**, 107–134.

RAFAL RD, GRIMM RJ (1981) Progressive supranuclear palsy: functional analysis of the response to methysergide and antiparkinsonian agents. *Neurology, New York*, **31**, 1507–1518.

RAFAL RD, POSNER MI, FRIEDMAN JH, INHOFF AW, BERNSTEIN E (1988) Orienting of visual attention in progressive supranuclear palsy. *Brain*, **111**, 267–280.

ROUZAUD M, DEGIOVANNI E, JOBARD P, GRAY F, DURAND JP (1974) L'ophtalmoplégie supra-nucléaire progressive (syndrome de Steele-Richardson-Olszewski): *nouvelle observation anatomo-clinique. Revue Neurologique*, **130**, 143–164.

SMITH WM, MCCRARY JW, SMITH KU (1960) Delayed visual feedback and behavior. *Science*, **132**, 1013–1014.

STEELE JC (1972) Progressive supranuclear palsy. *Brain*, **95**, 693–704.

STEELE JC, RICHARDSON JC, OLSZEWSKI J (1964) Progressive supranuclear palsy. *Archives of Neurology, Chicago*, **10**, 333–359.

TROOST BT, DAROFF RB (1977) The ocular motor defects in progressive supranuclear palsy. *Annals of Neurology*, **2**, 397–403.

WECHSLER D (1964) *Die Messung der Intelligenz Erwachsener*. 3. Aufl. Bern and Stuttgart: Huber.

WILCOXON F (1945) Individual comparisons by ranking methods. *Biometrics Bulletin*, **1**, 80–83.

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Brain (1991), **114**, 1473–1485

CORTICAL CONTROL OF REFLEXIVE VISUALLY-GUIDED SACCADES

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SUMMARY

Reflexive visually-guided saccade triggering may be facilitated or inhibited by the cerebral cortex. To study this control, saccades made towards suddenly appearing visual targets (saccade task) or away from them (antisaccade task) were recorded electro-oculographically in 45 patients with limited unilateral cerebral infarction. Lesions affected (1) the superior part of the angular gyrus (area 39 of Brodmann) in the posterior parietal cortex (PPC), (2) the dorsolateral prefrontal cortex (PFC) (area 46 of Brodmann), (3) the frontal eye field (FEF), or (4) the supplementary motor area (SMA). As these 4 types of lesions were located either in the right or the left cerebral hemisphere, patients were divided into 8 groups. Saccade latency, in the saccade task, and the percentage of errors (misdirected saccades made towards the visual target), in the antisaccade task, were compared in each group of patients with the values of 20 control subjects. In the saccade task, saccade latency was significantly increased bilaterally in the right PPC group. In the left PPC group, the increase in latency was less marked, and significant only for saccades made contralaterally to the lesion. In the different frontal groups, latency was unchanged or only slightly increased. These results confirm that the main area facilitating the triggering of reflexive visually-guided saccades is located in the PPC, in or near the superior part of the angular gyrus. The difference between right and left parietal lesions could be due to the predominance of the right hemisphere in the control of these saccades. In the antisaccade task, the percentage of errors was significantly increased bilaterally in both PFC groups compared with the control group and also to the FEF and SMA groups. These results suggest that the PFC is the main area in the cerebral hemisphere inhibiting reflexive visually-guided saccades.

INTRODUCTION

Cerebrally-triggered saccades may be intentional or reflexive (Tusa *et al.*, 1986). Reflexive visually-guided saccades are triggered by the sudden appearance of a target in the peripheral visual field. It has already been reported in man (Pierrot-Deseilligny *et al.*, 1987) and in the monkey (Lynch and McLaren, 1989) that latency of these saccades may be increased in certain subjects with posterior parietal lesions. However, no quantitative study of a group of patients with such lesions has been made to confirm these first results. Furthermore, the location within the posterior parietal cortex (PPC) of the area crucial for reflexive visually-guided saccades remains relatively unclear in man. In the monkey, there are also other areas in the frontal lobe active during visually-guided saccades: the frontal eye field (FEF) (Bruce and Goldberg, 1985), the supplementary motor area (SMA) (Schlag and Schlag-Rey, 1987) and the dorsolateral prefrontal cortex (PFC) (Boch and Goldberg, 1989; Funahashi *et al.*, 1989). The roles of these different frontal areas in the triggering of reflexive visually-guided saccades

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are still not clear. Lastly, besides excitatory mechanisms leading to the occurrence of reflexive visually-guided saccades, there are also inhibitory mechanisms to prevent such saccades when not required. In man, this inhibition could be controlled by the frontal lobe (Guitton *et al.*, 1985), but the specific frontal area involved in such a mechanism has yet to be determined. Therefore, 45 patients with limited unilateral infarction affecting one of the four main cortical oculomotor areas—i.e., PPC, PFC, FEF, SMA—were recorded electro-oculographically to study reflexive visually-guided saccades with two paradigms: the saccade task, testing the excitatory mechanisms involved in the triggering of these saccades, and the antisaccade task, testing inhibitory mechanisms.

PATIENTS AND METHODS

Subjects

The 45 patients in this study had recently developed a unilateral and relatively small cortical infarct. Those patients having a clinical history of, or signs of, another lesion in the same or opposite cerebral hemisphere were not included. The mean duration of the lesions was 48 days (SD = 47). The mean age of patients was 58 (SD = 14) yrs, namely analogous to that of control subjects (*see below*). There were only slight age variations between the different patient groups, defined below. All patients were right-handed, except for 4 who were left-handed, each of whom belonged to a different group (left PPC, right PFC, left PFC and right SMA groups).

Lesions, as ascertained by computerized (CT) scan and/or magnetic resonance imaging (MRI), had to be clearly visible and clearly limited to allow a degree of clinicoanatomical correlation. An example of such a lesion is given in fig. 1. Eye movement recording always followed radiological examination, at a mean interval of 17 (SD = 19) days. Lesions were outlined on a drawing corresponding to a horizontal section located approximately 24 mm below the upper limit of the cerebral hemispheres in accordance with the atlas by Matsui and Hirano (1978). This section, parallel to the canthomeatal line, as are sections of CT scan or MRI, has the advantage of showing the four studied oculomotor areas or the regions immediately below (fig. 2). As there were some slight variations (around the canthomeatal line) from one patient to another in the angle of horizontal sections used in CT scan or MRI, special care was taken to locate the precentral sulcus in each patient using the method proposed by Ebeling *et al.* (1986). After localization, which was possible for all patients, lesions were transposed with a sufficient degree of precision onto the chosen horizontal section.

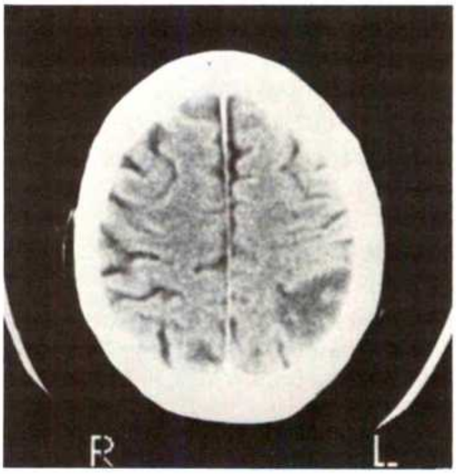

FIG. 1. CT scan of a patient with left posterior parietal lesion. This is a horizontal section at the level of the section chosen for the drawings in fig. 2.

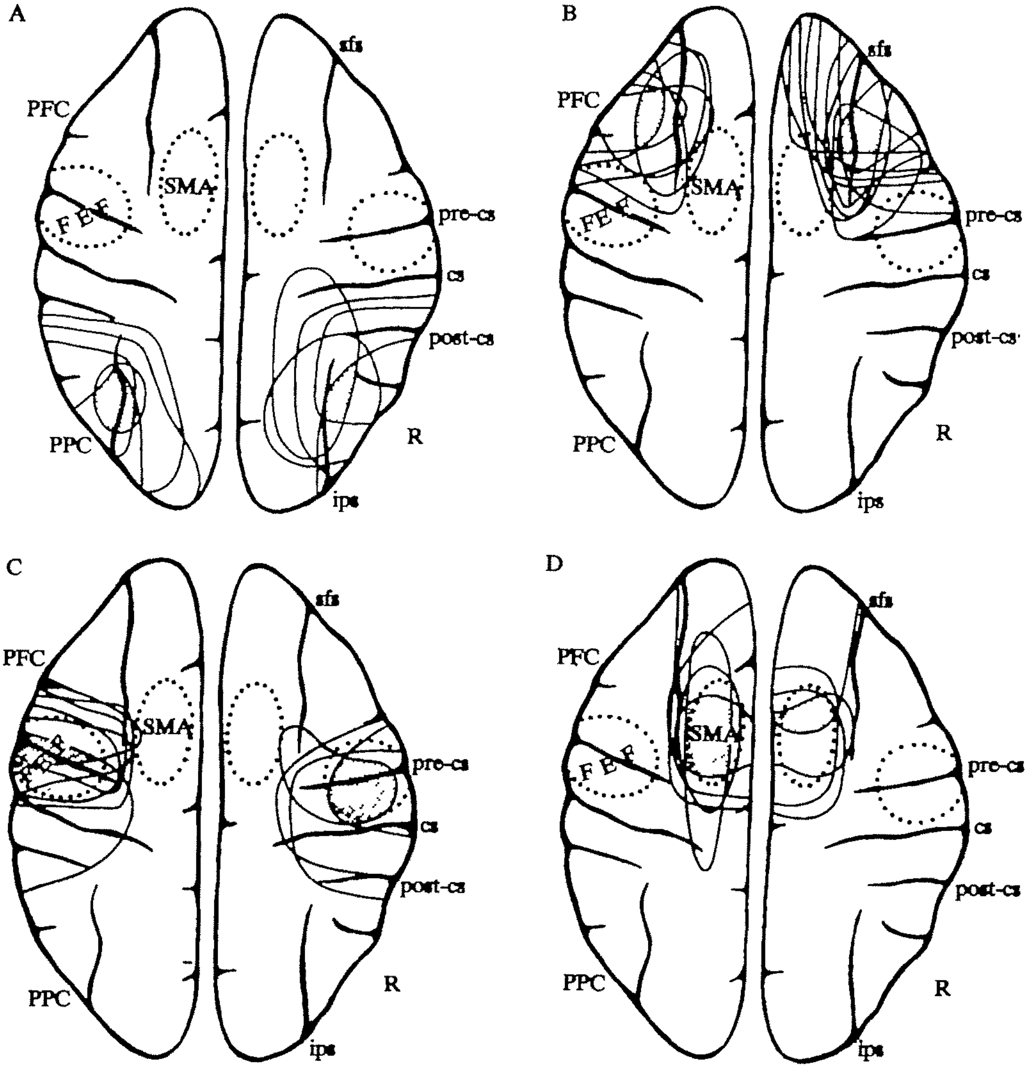

Fig. 2. Lesions in the patients Lesions are drawn on a horizontal section passing 24 mm below the upper limit of the cerebral hemispheres. A, B, C and D, lesions affecting the PPC, the PFC, the FEF and the SMA, respectively. Each thin line corresponds to a different lesion. In each group, the grey zone is the common area of damage. The dotted lines indicate the approximate limits of the FEF and the SMA. cs = central sulcus; FEF = frontal eye field, ips = intraparietal sulcus; PFC = prefrontal cortex; post-cs = postcentral sulcus; PPC = posterior parietal cortex; pre-cs = precentral sulcus; R = right, sfs = superior frontal sulcus; SMA = supplementary motor area.

Ten patients had lesions affecting the PPC, always damaging the superior part of the angular gyrus (area 39 of Brodmann), i.e., the area located just laterally to the posterior portion of the intraparietal sulcus (fig. 2A). This part of the parietal lobe was chosen as the area of common damage within the PPC groups since it might be involved in both visual attention (Eidelberg and Galaburda, 1984) and ocular motor control (Pierrot-Deseilligny *et al.*, 1986). Lesions affecting the PPC were all located above or beside the optic radiations and there were no visual defects using Goldmann's perimetry in these patients. Five patients had a lesion on the right side (right PPC group) and 5 on the left (left PPC group).

Sixteen patients had lesions affecting the PFC, always damaging the area located just laterally to the superior frontal sulcus and anteriorly to the precentral sulcus, i.e., the superior part of area 46 of Brodmann (fig. 2B). This part of the prefrontal cortex was chosen as the area of common damage within the PFC groups since it could correspond to the part of the dorsolateral prefrontal cortex involved in saccade control in the monkey (area 46 of Walker) (Goldman-Rakic, 1987; Rajkowska and Goldman-Rakic, 1990). The posterior and the medial extensions of the lesions were slight, to avoid substantial combined damage to the nearby FEF and SMA. Ten patients had a lesion on the right side (right PFC group) and 6 on the left (left PFC group).

Ten patients had lesions affecting the FEF (fig. 2C). This area has been defined in man by stimulation (Penfield and Boldrey, 1937; Godoy *et al.*, 1990) and PET scan studies (Melamed and Larsen, 1979; Fox *et al.*, 1985). It appears to be centred on the precentral sulcus at the level of the second frontal gyrus, involving both the posterior extremity of this gyrus and the adjacent motor area. The anterior and medial extensions of the lesions were slight, to avoid substantial combined damage to the nearby PFC and SMA. Four patients had a lesion on the right side (right FEF group) and 6 on the left (left FEF group).

Nine patients had lesions affecting the SMA, i.e., located just medial to the superior frontal sulcus and anterior to the precentral sulcus (fig. 2D). This area has been defined in man by PET scan studies (Melamed and Larsen, 1979; Fox *et al.*, 1985). The lateral extension of the lesions was slight, to avoid substantial combined damage to the nearby PFC and FEF. Four patients had a lesion on the right side (right SMA group) and 5 on the left (left SMA group).

A control group of 20 subjects (mean age = 59, SD = 9, yrs) was studied with the same paradigms as the patients. The control subjects had no history of neurological disorder and were normal on neurological examination.

Eye movement recordings

Eye movements were recorded by d.c. electro-oculography in complete darkness with 4 electrodes (2 horizontal temporal and 2 vertical on one eye). The subject was located 80 cm from the stimulation points. The head was immobilized by a head-rest with a restraining mechanism at the temples. A 15 min period was allowed for adaptation to darkness before the recording session. The session began with a calibration employing the lateral targets to be used in the tests. The lateral target was 3° in size and 9 cd/m^2 in luminance.

In the saccade task (fig. 3A), the subject fixed a central fixation point which disappeared 200 ms (gap) before the appearance of a lateral target, which had to be fixed as quickly as possible. The lateral target occurred 25° away from the central point, either right or left, with unpredictable time and direction. Latency was the time between the onset of the lateral target and the start of the saccade. Latencies under 50 ms, suggesting an anticipated saccade (Smit and Van Gisbergen, 1989), or above 800 ms, probably due to temporary inattention, were excluded from the calculations. Saccades with such short or long latency were,

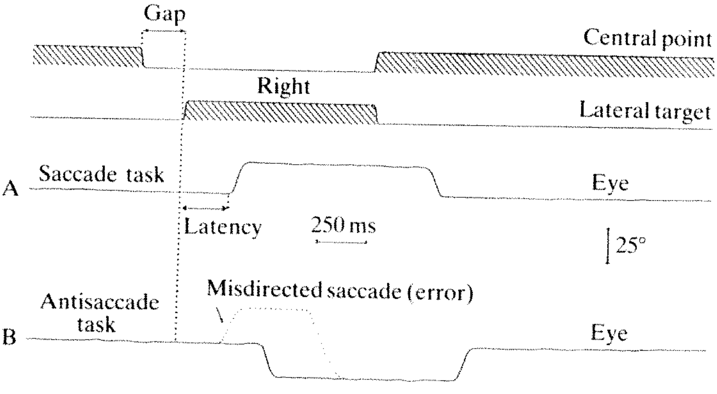

FIG. 3. Paradigms for saccade and antisaccade tasks.

in fact, rare in both control subjects and patients. Right and left saccade latencies were calculated by averaging 30 measurements in each direction.

In the antisaccade task (fig. 3B), the stimuli were the same as in the saccade task but the subject was required to look in the opposite direction to the target, without looking at it. When the subject looked first at the target or in the direction of the target, this constituted an error. The percentage of errors was measured for each lateral direction (30 stimulations in each case). Latency of antisaccades was not analysed, both because the instruction was not given to perform these saccades as quickly as possible and because antisaccade amplitude was rather variable.

Statistical analysis

Comparisons of saccade latencies between each group of patients and the control group were performed by analysis of variance followed by multiple comparisons (Student-Newman-Keuls test). As the percentage of error distribution in the antisaccade task was not normal, a nonparametric test (Kruskal-Wallis test) was used to compare these values for each patient group with those of control subjects. For further comparisons concerning the percentage of errors between two groups of patients, another nonparametric test (Mann-Whitney) was used. Significance was accepted at the $P < 0.05$ level.

RESULTS

Individual data are shown in figs 4 and 5 and mean results are given in the Table. Latency of reflexive visually-guided saccades was significantly increased bilaterally in the right PPC group compared with the control group. In the left PPC group, the increase in latency was less marked, and significant only for saccades made contralaterally to the lesion. In the different frontal groups, latency was normal or slightly increased, but not significantly.

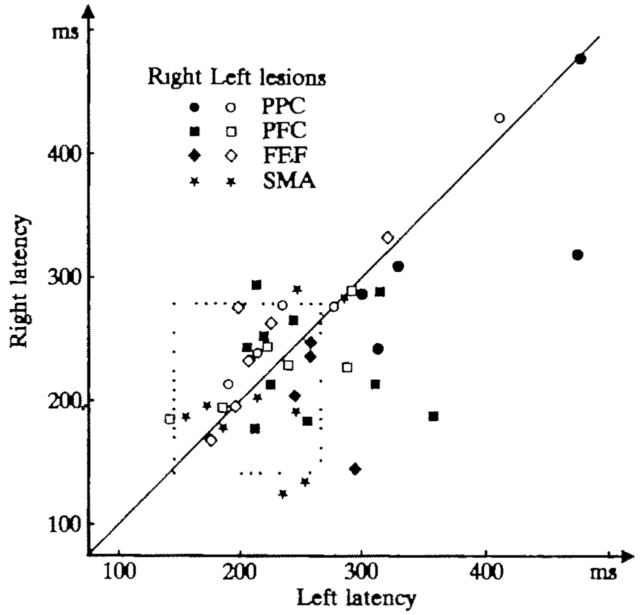

FIG. 4. Individual latencies (saccade task). Each symbol represents a patient. The dotted lines indicate the limits of the normal range. FEF = frontal eye field; PFC = prefrontal cortex; PPC = posterior parietal cortex; SMA = supplementary motor area.

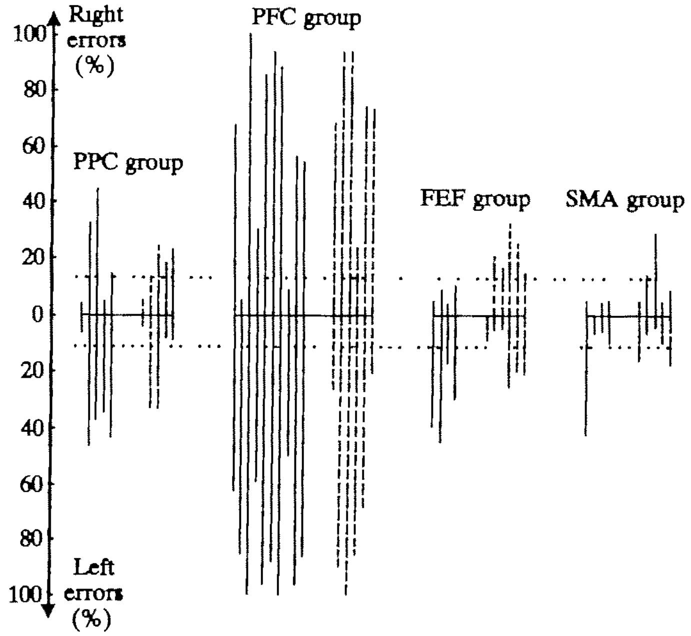

FIG. 5. Individual percentages of error (antisaccade task). Each vertical line represents a patient and each horizontal dotted line the mean of the control group. FEF = frontal eye field; PFC = prefrontal cortex; PPC = posterior parietal cortex; SMA = supplementary motor area. Continuous lines = right lesions; broken lines = left lesions.

TABLE. MEAN VALUES OF THE DIFFERENT LESION GROUPS

	Visually-guided saccades Latency: mean (ms) ± SD		*Antisaccades Percentage of errors. mean (range)*	
	Right	*Left*	*Right*	*Left*
Control group (n = 20)	208 ± 35	206 ± 30	14 (0–38)	12 (0–32)
PPC lesions				
Right (n = 5)	324 ± 89^{b}	380 ± 88^{b}	20 (4–45)	34 (7–46)
Left (n = 5)	284 ± 83^{a}	266 ± 86	17 (5–23)	18 (4–33)
PFC lesions				
Right (n = 10)	223 ± 50	255 ± 53	59 (5–100)^{c,e,h}	81 (50–100)^{d,g,i}
Left (n = 6)	226 ± 41	227 ± 59	72 (25–95)^{c,f,h}	65 (26–100)^{c,e,i}
FEF lesions				
Right (n = 4)	206 ± 46	264 ± 22	7 (5–10)	31 (18–45)
Left (n = 6)	245 ± 60	220 ± 54	18 (0–32)	14 (5–27)
SMA lesions				
Right (n = 4)	188 ± 73	237 ± 21	4 (0–5)	16 (5–43)
Left (n = 5)	206 ± 47	209 ± 57	12 (5–29)	10 (1–18)

[a,b] Analysis of variance (followed by Student-Newman-Keuls test) was used for the comparison of latency of each patient group with that of the control group; a and b correspond to statistical levels of $P < 0.05$ and $P < 0.005$, respectively. [c,d] Kruskal-Wallis test was used for the comparison of percentage of errors of each patient group with that of the control group; c and d correspond to statistical levels of $P < 0.01$ and $P < 0.005$, respectively. [e,f,g] Mann-Whitney test was used for the comparison of the percentage of errors of each PFC group with that of the corresponding FEF group (with lesions in the same cerebral hemisphere), [e, f, g] correspond to statistical levels of $P < 0.02$, $P < 0.01$ and $P < 0.005$, respectively. [h,i] Mann-Whitney test was used for the comparison of the percentage of errors of each PFC group with that of the corresponding SMA group (with lesions in the same cerebral hemisphere); [h, i] correspond to statistical levels of $P < 0.01$ and $P < 0\ 005$, respectively.

The percentage of errors in the antisaccade task was significantly increased bilaterally in both PFC groups compared with the control group (*see* Table). In the other groups, the percentage of errors was only slightly increased, but not significantly. To ensure that the high percentage of errors observed in the PFC groups was specific to lesions of this area, i.e., not due to damage to other nearby oculomotor areas, further comparisons were performed between each PFC group and the FEF group or SMA group corresponding to the same cerebral hemisphere. The percentage of errors was always more significantly increased in the PFC group than in the FEF or SMA groups (*see* Table).

DISCUSSION

Patients with right posterior parietal lesions showed a bilateral increase in latency of reflexive visually-guided saccades, whereas patients with right or left prefrontal lesions showed a bilateral increase in the percentage of unwanted saccades. These results suggest a lack of excitation in the former case and a lack of inhibition in the latter case during reflexive visually-guided saccade initiation. These two points will be dealt with successively.

Excitatory control of reflexive visually-guided saccades

All cerebrally-triggered saccades are initiated either by the superior colliculus or the FEF (Schiller *et al.*, 1980) (fig. 6). The superior colliculus is involved in the triggering of reflexive visually-guided saccades, since lesions affecting this structure result in increased saccade latency in the monkey (Hikosaka and Wurtz, 1986; Schiller *et al.*, 1987). The superior colliculus receives direct afferences from the FEF (Leichnetz *et al.*,

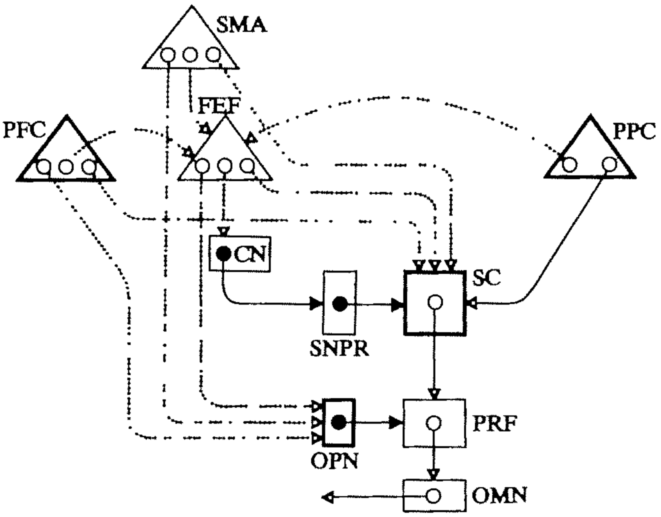

FIG. 6. Hypothetical circuitry involved in reflexive visually-guided saccade triggering White circle with continuous line = excitatory neuron, black circle = inhibitory neuron; white circle with dotted line = action poorly understood. CN = caudate nucleus; FEF = frontal eye field, OMN = ocular motor nucleus; OPN = omnipause neuron; PFC = prefrontal cortex; PPC = posterior parietal cortex; PRF = premotor reticular formation; SC = superior colliculus; SMA = supplementary motor area, SNPR = substantia nigra pars reticulata.

1981; Fries, 1984, 1985; Komatsu and Suzuki, 1985; Huerta *et al.*, 1986; Segraves and Goldberg, 1987; Stanton *et al.*, 1988), which also projects directly onto the brainstem reticular formations involved in saccade generation (Leichnetz *et al.*, 1984; Stanton *et al.*, 1988). However, cortical lesions affecting the FEF in the monkey (Deng *et al.*, 1986; Schiller *et al.*, 1987) or in man (Sharpe, 1986; Pierrot-Deseilligny *et al.*, 1987) result in no increase, or only an increase in contralateral reflexive visually-guided saccade latency. Our patients with a cortical FEF lesion showed only a slight increase in saccade latency. Therefore, the FEF does not appear to be crucial for the initiation of reflexive visually-guided saccades. The PFC (Boch and Goldberg, 1989) and the SMA (Schlag and Schlag-Rey, 1987) also contain cells active just prior to visually-guided saccades, and they both project onto the superior colliculus and the premotor reticular formations (DeVito and Smith, 1959; Leichnetz *et al.*, 1981, 1987; Shook *et al.*, 1988). The increase in latency was slight in the PFC and SMA groups. These results show that the PFC and the SMA are also not crucial for the triggering of reflexive visually-guided saccades.

It would appear, on the other hand, that the PPC is involved in the triggering of reflexive visually-guided saccades. In the monkey, this area, in particular the lateral intraparietal (LIP) area, contains visuomotor cells active during visually-guided saccades (Lynch *et al.*, 1977; Andersen *et al.*, 1987; Colby *et al.*, 1988; Gnadt and Andersen, 1988). Area LIP projects directly onto the superior colliculus (Fries, 1984; Weber and Yin, 1984; Lynch *et al.*, 1985) and the FEF (Barbas and Mesulam, 1981; Cavada and Goldman-Rakic, 1989; Neal *et al.*, 1990). Stimulation of area LIP elicits saccades (Shibutani *et al.*, 1984), which no longer occur after damage to the superior colliculus (Keating *et al.*, 1983). Unilateral lesions affecting the PPC in the monkey often result in increased latency of reflexive visually-guided saccades, either bilaterally or contralaterally to the lesion (Lynch and McLaren, 1989).

In man, it has been reported that bilateral lesions, affecting both the PPC and the FEF, severely impair the initiation of all cerebrally-triggered saccades (intentional as well as reflexive) (Pierrot-Deseilligny *et al.*, 1988). Therefore, saccade triggering could originate from these two cortical areas. Isolated bilateral posterior parietal lesions appear to affect mainly the triggering of visually-guided saccades (Pierrot-Deseilligny *et al.*, 1986 and unpublished data). A unilateral posterior parietal lesion often results in a bilateral increase in reflexive visually-guided latency (Pierrot-Deseilligny *et al.*, 1987). More recently, it has been reported that saccade latency in a right parietal group of 7 patients was only slightly increased for leftward saccades (Nagel-Leiby *et al.*, 1990). However, because of differences between the patients included in this group and those reported here, it is difficult to compare the two studies: in particular, the aetiology was rarely an infarction in this previous study, the age of lesions (21 months on average) was much greater than here, and these lesions did not always affect the superior part of area 39 of Brodmann, unlike those in our study. Our results showed a marked and significant bilateral increase in reflexive visually-guided saccade latency in patients with a right posterior parietal lesion. This suggests that, in the normal state, the right PPC facilitates the triggering of reflexive visually-guided saccades. The increase in latency was less marked in our patients with a left posterior parietal lesion, and significant only for saccades made contralaterally to the lesion. This difference between right and left parietal lesions might be explained by a certain specialization of the right hemisphere, and more precisely of the right parietal lobe, for certain functions, such as visuospatial function (Mesulam, 1981; Weintraub and Mesulam, 1987) and the control of eye deviation (Meador *et al.*, 1989) and of memory-guided saccades (Pierrot-Deseilligny *et al.*, 1991). Such specialization could also involve the triggering of reflexive visually-guided saccades.

The precise role of the parietal lobe in reflexive visually-guided saccade initiation remains hypothetical. It may first be questioned whether a disorder in the disengagement of attention to the central fixation point is involved in patients with parietal lesions. Such a disorder could, indeed, contribute to the increase in saccade latency. This question may be raised because (1) a disengagement of attention appears to be required prior to a shift of gaze towards another point of interest (the lateral target) (Fischer, 1987), and (2) the parietal lobe could be involved in such a disengagement of attention (Posner *et al.*, 1984; Posner and Petersen, 1990). However, if a disengagement of attention may be internally triggered by the parietal lobe when the central fixation point remains switched on, this disengagement may also be externally triggered by the offset of the central point. When, moreover, the offset of the central fixation point precedes by 200 ms the onset of the lateral target as in our saccade task, this gap results in, or at least contributes to, the disengagement of attention (Fischer and Breitmeyer, 1987; Braun and Breitmeyer, 1990). As this externally triggered disengagement of attention existed in all our patients, the consequence on saccade latency of a possible disorder in the internally triggered parietal disengagement of attention was probably limited here.

As an alternative to the attention disorder discussed immediately above, or in combination with it, it may be that the impairment of another mechanism existed to explain increased saccade latency in our patients with parietal lesions. This mechanism could be related to the perception of the lateral target. However, the disorder of visual attention existing in visual neglect does not appear to be responsible for the increase in reflexive visually-guided saccade latency: this increase is usually bilateral in patients with unilateral parietal lesions, whereas visual neglect is inconstant in the same patients and, when present, largely contralateral to the lesion (Pierrot-Deseilligny *et al.*, 1987). In the monkey, the PPC contains certain cells (especially in area 7a) involved in visual attention (Bushnell *et al.*, 1981), and other cells (mainly in area LIP) involved in motor planning of visually-guided saccades (Andersen *et al.*, 1987; Andersen, 1989). This suggests that visual attention and visually-guided saccade initiation could be controlled by close but distinct parietal cells. In man, a cytoarchitectonic study has suggested that the parietal area that plays a role in visual attention could be located in the superior part of the angular gyrus and the adjacent intraparietal sulcus (Eidelberg and Galaburda, 1984). This area was, here, the commonly damaged area within the PPC. Our data support the hypothesis that such an area, or an area located in close proximity, also controls reflexive visually-guided saccade initiation.

Finally, the impairment of another parietal process, different from that which is impaired in visual neglect, could be mainly responsible for increased saccade latency in patients with parietal lesions. It should be noted that the location of the visual target was predetermined in our saccade task, since it varied randomly between only two positions. We suggest that the role of the parietal lobe in saccade initiation during such a task is to select and pre-excite (or disinhibit) certain cells of the superior colliculus, i.e., those which have the appropriate movement field corresponding to the saccade to be performed (Pierrot-Deseilligny, 1989, 1991). It has already been suggested that a similar mechanism is involved at the level of the superior colliculus during the preparation of predictive saccades (Munoz and Guitton, 1989). Area LIP in the monkey, involved in motor planning during visually-guided saccades (*see above*), appears to be a likely candidate to perform the parietal facilitation in our saccade task. This parietal influence could be conducted through the superior colliculus by the direct parietocollicular tract rather than through the FEF, since saccade latency was much less increased after FEF lesions than after PPC lesions (*see* Table). Other studies are required, however, to determine the precise role(s) of the parietal lobe in the preparation of reflexive visually-guided saccades.

Inhibitory control of reflexive visually-guided saccades

An increase in the percentage of unwanted reflexive visually-guided saccades in the antisaccade task may be considered as a deficit in the inhibitory control of these saccades. First, inhibition may occur in the superior colliculus, which receives an inhibitory afference from the substantia nigra pars reticulata (Hikosaka, 1989; Hikosaka *et al.*, 1989) and also, perhaps, direct frontal inhibitory afferences (Segraves and Goldberg, 1987). Secondly, inhibition may be exerted via the omnipause cells, inhibiting the premotor reticular formations (Büttner-Ennever *et al.*, 1988). Though the pathways projecting onto these two types of inhibitory neurons are not yet well known, their origin could be frontal. Indeed, it has been reported that patients with variously located focal frontal lesions (Guitton *et al.*, 1985) and with frontal lobe-like dysfunction (Pierrot-Deseilligny *et al.*, 1989) showed an abnormally high percentage of errors in the antisaccade task.

To localize more precisely the origin of this inhibitory control in the frontal lobe, we studied patients with lesions centred on one of the 3 frontal oculomotor areas (PFC, FEF, SMA). Special attention was paid to the PFC because electrophysiological data in the monkey suggest that this area is involved in such inhibitory control (Goldman-Rakic, 1987; Boch and Goldberg, 1989; Funahashi *et al.*, 1989, 1990). In the monkey, the PFC is located just anteriorly and contiguous to the FEF (Joseph and Barone, 1987; Boch and Goldberg, 1989). The PFC in man, corresponding to area 46 of Walker in the monkey, could be located in area 46 of Brodmann, i.e., also just anteriorly to the FEF (Goldman-Rakic, 1987). In man, area 46 lies within the second and third frontal gyri but is more extensive in the second frontal gyrus. Lesions in our PFC groups always damaged the second frontal gyrus. We also recorded a few patients with lesions restricted to the third frontal gyrus, but their number was too small to constitute groups. However, their individual percentages of errors in the antisaccade task were similar to those of control subjects (Pierrot-Deseilligny, unpublished data). This supports the fact that area 46 could be restricted to the second frontal gyrus in man (Rajkowska and Goldman-Rakic, 1990). In our patients, high percentages of errors existed bilaterally only in right and left PFC groups. In these groups, the increase in errors was significant not only compared with control subjects but also to the FEF or SMA groups. It may therefore be deduced that the inhibitory control involved in the antisaccade task originates mainly from the PFC. Furthermore, the fact that a slight and nonsignificant increase in errors existed in the other frontal oculomotor areas suggests that this inhibitory control is exerted directly on subcortical structures rather than via the FEF or the SMA. As the PFC projects onto the superior colliculus directly (Goldman and Nauta, 1976; Leichnetz *et al.*, 1981; Fries, 1985) and also probably via the basal ganglia (Goldman and Nauta, 1977), and onto the region of the omnipause neurons (Leichnetz *et al.*, 1987), these different projections could control the inhibition of unwanted reflexive visually-guided saccades. The PPC and the PFC would, therefore, appear to be the most important areas involved in the control of reflexive visually-guided saccades in man, facilitating or inhibiting their triggering, respectively.

REFERENCES

Andersen RA (1989) Visual and eye movement functions of the posterior parietal cortex. *Annual Review of Neuroscience*, **12**, 377–403

Andersen RA, Essick GK, Siegel RM (1987) Neurons of area 7 activated by both visual stimuli and oculomotor behavior. *Experimental Brain Research*, **67**, 316–322.

Barbas H, Mesulam M-M (1981) Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *Journal of Comparative Neurology*, **200**, 407–431.

Boch RA, Goldberg ME(1989) Participation of prefrontal neurons in the preparation of visually guided eye movements in the rhesus monkey. *Journal of Neurophysiology*, **61**, 1064–1084.

Braun D, Breitmeyer BG (1990) Effects of reappearance of fixated and attended stimuli upon saccadic reaction time. *Experimental Brain Research*, **81**, 318–324.

Bruce CJ, Goldberg ME (1985) Primate eye fields. I. Single neurons discharging before saccades *Journal of Neurophysiology*, **53**, 603–635.

Bushnell MC, Goldberg ME, Robinson DL (1981) Behavioral enhancement of visual responses in monkey cerebral cotex. I. Modulation in posterior parietal cortex related to selective visual attention. *Journal of Neurophysiology*, **46**, 755–772.

Büttner-Ennever JA, Cohen B, Pause M, Fries W (1988) Raphe nucleus of the pons containing omnipause neurons of the oculomotor system in the monkey, and its homologue in man. *Journal of Comparative Neurology*, **267**, 307–321.

Cavada C, Goldman-Rakic PS (1989) Posterior parietal cortex in rhesus monkey: II. Evidence for segregated corticocortical networks linking sensory and limbic areas with the frontal lobe. *Journal of Comparative Neurology*, **287**, 422–445.

Colby CL, Duhamel J-R, Goldberg ME (1988) Response properties of neurons in macaque intraparietal sulcus. *Society for Neuroscience Abstracts*, **14**, 11.

Deng S-Y, Goldberg ME, Segraves MA, Ungerleider LG, Mishkin M (1986) The effect of unilateral ablation of the frontal eye fields on saccadic performance in the monkey. In: *Adaptive Processes in Visual and Oculomotor Systems*. Edited by E. L. Keller and D. S Zee. Oxford: Pergamon Press, pp. 201–208.

DeVito JL, Smith OA (1959) Projections from the mesial frontal cortex (supplementary motor area) to the cerebral hemispheres and brain stem of the Macaca mulatta. *Journal of Comparative Neurology*, **111**, 261–277.

Ebeling U, Huber P, Reulen HJ (1986) Localization of the precentral gyrus in the computed tomogram and its clinical application. *Journal of Neurology*, **233**, 73–76.

Eidelberg D, Galaburda AM (1984) Inferior parietal lobule: divergent architectonic asymmetries in the human brain. *Archives of Neurology, Chicago*, **41**, 843–852.

Fischer B (1987) The preparation of visually guided saccades. *Reviews of Physiology, Biochemistry and Pharmacology*, **106**, 1–35.

Fischer B, Breitmeyer B (1987) Mechanisms of visual attention revealed by saccadic eye movements. *Neuropsychologia*, **25**, 73–83.

Fox PT, Fox JM, Raichle ME, Burde RM (1985) The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomographic study. *Journal of Neurophysiology*, **54**, 348–369.

Fries W (1984) Cortical projections to the superior colliculus in the macaque monkey: a retrograde study using horseradish peroxidase. *Journal of Comparative Neurology*, **230**, 55–76.

Fries W (1985) Inputs from motor and premotor cortex to the superior colliculus of the macaque monkey. *Behavioural Brain Research*, **18**, 95–105.

Funahashi S, Bruce CJ, Goldman-Rakic PS (1989) Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *Journal of Neurophysiology*, **61**, 331–349

Funahashi S, Bruce CJ, Goldman-Rakic PS (1990) Visuospatial coding in primate prefrontal neurons revealed by oculomotor paradigms. *Journal of Neurophysiology*, **63**, 814–831.

Gnadt JW, Andersen RA (1988) Memory related motor planning activity in posterior parietal cortex of macaque. *Experimental Brain Research*, **70**, 216–220.

Godoy J, Lüders H, Dinner DS, Morris HH, Wyllie E (1990) Versive eye movements elicited by cortical stimulation of the human brain. *Neurology, Cleveland*, **40**, 296–299.

Goldman PS, Nauta WJH (1976) Autoradiographic demonstration of a projection from prefrontal association cortex to the superior colliculus in the rhesus monkey. *Brain Research, Amsterdam*, **116**, 145–149.

Goldman PS, Nauta WJH (1977) An intricately patterned prefronto-caudate projection in the rhesus monkey. *Journal of Comparative Neurology*, **171**, 369–385.

Goldman-Rakic PS (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: *Handbook of Physiology*, Section 1, Volume 5, Part I. Edited by V. B. Mountcastle. Bethesda, MD: American Physiological Society, pp. 373–417.

Guitton D, Buchtel HA, Douglas RM (1985) Frontal lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Experimental Brain Research*, **58**, 455–472.

Hikosaka O (1989) Role of basal ganglia in saccades. *Revue Neurologique*, **145**, 580–586.

Hikosaka O, Wurtz RH (1986) Saccadic eye movements following injection of lidocaine into the superior colliculus. *Experimental Brain Research*, **61**, 531–539.

Hikosaka O, Sakamoto M, Usui S (1989) Functional properties of monkey caudate neurons. I. Activities related to saccadic eye movement. II. Visual and auditory responses. III. Activities related to expectation of target and reward. *Journal of Neurophysiology*, **61**, 780–832.

Huerta MF, Krubitzer LA, Kaas JH (1986) Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys, and macaque monkeys: I. Subcortical connections. *Journal of Comparative Neurology*, **253**, 415–439.

Joseph JP, Barone P (1987) Prefrontal unit during a delayed oculomotor task in the monkey. *Experimental Brain Research*, **67**, 460–468.

Keating EG, Gooley SG, Pratt SE, Kelsey JE (1983) Removing the superior colliculus silences eye movements normally evoked from stimulation of the parietal and occipital eye fields. *Brain Research, Amsterdam*, **269**, 145–148.

Komatsu H, Suzuki H (1985) Projections from the functional subdivisions of the frontal eye field to the superior colliculus in the monkey. *Brain Research, Amsterdam*, **327**, 324–327.

Leichnetz GR, Spencer RF, Hardy SGP, Astruc J (1981) The prefrontal corticotectal projection in the monkey; an anterograde and retrograde horseradish peroxidase study. *Neuroscience*, **6**, 1023–1041.

Leichnetz GR, Spencer RF, Smith DJ (1984) Cortical projections to nuclei adjacent to the oculomotor complex in the medial dien-mesencephalic tegmentum in the monkey. *Journal of Comparative Neurology*, **228**, 359–387.

Leichnetz GR, Gonzalo-Ruiz A, DeSalles AAF, Hayes RL (1987) The frontal eye field and prefrontal cortex project to the paramedian pontine reticular formation in the cat. *Brain Research, Amsterdam*, **416**, 195–199.

Lynch JC, Mountcastle VB, Talbot WH, Yin TCT (1977) Parietal lobe mechanisms for directed visual attention. *Journal of Neurophysiology*, **40**, 362–389.

Lynch JC, Graybiel AM, Lobeck LJ (1985) The differential projection of two cytoarchitectonic subregions of the inferior parietal lobule of macaque upon the deep layers of the superior colliculus. *Journal of Comparative Neurology*, **235**, 241–254.

Lynch JC, McLaren JW (1989) Deficits of visual attention and saccadic eye movements after lesions of parietooccipital cortex in monkeys. *Journal of Neurophysiology*, **61**, 74–90.

Matsui T, Hirano A (1978) *An Atlas of the Human Brain for Computerized Tomography*. Tokyo: Igaku-Shoin.

Meador KJ, Loring DW, Lee GP, Brooks BS, Nichols FT, Thompson EE *et al.* (1989) Hemisphere asymmetry for eye gaze mechanisms. *Brain*, **112**, 103–111.

Melamed E, Larsen B (1979) Cortical activation pattern during saccadic eye movements in humans: localization by focal cerebral blood flow increases. *Annals of Neurology*, **5**, 79–88.

Mesulam M-M (1981) A cortical network for directed attention and unilateral neglect. *Annals of Neurology*, **10**, 309–325.

Munoz DP, Guitton D (1989) Fixation and orientation control by the tecto-reticulo-spinal system in the cat whose head is unrestrained. *Revue Neurologique*, **145**, 567–579.

Nagel-Leiby S, Buchtel HA, Welch KMA (1990) Cerebral control of directed visual attention and orienting saccades. *Brain*, **113**, 237–276.

Neal JW, Pearson RCA, Powell TPS (1990) The ipsilateral corticocortical connections of area 7 with the frontal lobe in the monkey. *Brain Research, Amsterdam*, **509**, 31–40.

Penfield W, Boldrey E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, **60**, 389–443.

Pierrot-Deseilligny C (1989) Contrôle cortical des saccades. *Revue Neurologique*, **145**, 596–604.

Pierrot-Deseilligny C (1991) Cortical control of saccades. *Neuro-Opthalmology*, **11**, 63–75.

Pierrot-Deseilligny C, Gray F, Brunet P (1986) Infarcts of both inferior parietal lobules with impairment of visually guided eye movements, peripheral visual inattention and optic ataxia. *Brain*, **109**, 81–97.

Pierrot-Deseilligny C, Rivaud S, Penet C, Rigolet M-H (1987) Latencies of visually guided saccades in unilateral hemispheric cerebral lesions. *Annals of Neurology*, **21**, 138–148.

Pierrot-Deseilligny C, Gautier J-C, Loron P (1988) Acquired ocular motor apraxia due to bilateral frontoparietal infarcts. *Annals of Neurology*, **23**, 199–202.

Pierrot-Deseilligny C, Rivaud S, Pillon B, Fournier E, Agid Y (1989) Lateral visually-guided saccades in progressive supranuclear palsy. *Brain*, **112**, 471–487.

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y (1991) Cortical control of memory-guided saccades in man. *Experimental Brain Research*, **83**, 607–617.

Posner MI, Walker JA, Friedrich FJ, Rafal RD (1984) Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience*, **4**, 1863–1874.

Posner MI, Petersen SE (1990) The attention system of the human brain. *Annual Review of Neuroscience*, **13**, 25–42.

Rajkowska G, Goldman-Rakic PS (1990) Cytoarchitectonic remapping of areas 9 and 46 in the human prefrontal cortex. *Society for Neuroscience Abstracts*, **16**, 1093.

Schiller PH, True SD, Conway JL (1980) Deficits in eye movements following frontal eye-field and superior colliculus ablations. *Journal of Neurophysiology*, **44**, 1175–1189.

Schiller PH, Sandell JH, Maunsell JHR (1987) The effect of frontal eye field and superior colliculus lesions on saccadic latencies in the rhesus monkey. *Journal of Neurophysiology*, **57**, 1033–1049.

Schlag J, Schlag-Rey M (1987) Evidence for a supplementary eye field. *Journal of Neurophysiology*, **57**, 179–200.

Segraves MA, Goldberg ME (1987) Functional properties of corticotectal neurons in the monkey's frontal eye field. *Journal of Neurophysiology*, **58**, 1387–1419.

Sharpe JA (1986) Adaptation to frontal lobe lesions. In: *Adaptive Processes in Visual and Oculomotor Systems*. Edited by E. L. Keller and D. S. Zee. Oxford: Pergamon Press, pp. 239–246.

Shibutani H, Sakata H, Hyvärinen J (1984) Saccade and blinking evoked by microstimulation of the posterior parietal association cortex of the monkey. *Experimental Brain Research*, **55**, 1–8.

Shook BL, Schlag-Rey M, Schlag J (1988) Direct projection from the supplementary eye field to the nucleus raphe interpositus. *Experimental Brain Research*, **73**, 215–218.

Smit AC, Gisbergen JAM Van (1989) A short-latency transition in saccade dynamics during square-wave tracking and its significance for the differentiation of visually-guided and predictive saccades. *Experimental Brain Research*, **76**, 64–74.

Stanton GB, Goldberg ME, Bruce CJ (1988) Frontal eye field efferents in the macaque monkey: I. Subcortical pathways and topography of striatal and thalamic terminal fields. II. Topography of terminal fields in midbrain and pons. *Journal of Comparative Neurology*, **271**, 473–506.

Tusa RJ, Zee DS, Herdman SJ (1986) Effect of unilateral cerebral cortical lesions on ocular motor behavior in monkeys: saccades and quick phases. *Journal of Neurophysiology*, **56**, 1590–1625.

Weber JT, Yin TCT (1984) Subcortical projections of the inferior parietal cortex (area 7) in the stump-tailed monkey. *Journal of Comparative Neurology*, **224**, 206–230.

Weintraub S, Mesulam M-M (1987) Right cerebral dominance in spatial attention: further evidence based on ipsilateral neglect. *Archives of Neurology, Chicago*, **44**, 621–625.

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INCREMENT-THRESHOLD SPECTRAL SENSITIVITY IN BLINDSIGHT

EVIDENCE FOR COLOUR OPPONENCY

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SUMMARY

In the circumscribed visual field defects of 3 patients, increment-threshold spectral sensitivity was measured with a guessing paradigm. Nine 116′, 200 ms narrowband stimuli with maximum transmission between 450 and 660 nm were presented on a white background of photopic or scotopic luminance. Sensitivity measured in the blind field was compared with that at matched positions in the patients' normal hemifield, and with that at corresponding positions in 2 control subjects. Results show that spectral sensitivity in the blind field, albeit reduced by up to 1 log unit, shows normal dependence on adaptation level, reflecting rod activity under scotopic, and cone activity under photopic conditions. Characteristic discontinuities in the spectral sensitivity curve seen under light adaptation are evidence for colour-opponent processes, presumably involving primate beta retinal ganglion cells.

INTRODUCTION

Damage to the striate cortex or its afferents from the lateral geniculate nucleus produces homonymous visual field defects whose perimetrically defined extent and density reflect the site, extent and completeness of the lesion. Even in clinically absolute defects in which the patients do not experience visual sensation, residual visual abilities have been demonstrated and termed blindsight (Sanders *et al.*, 1974; Weiskrantz *et al.*, 1974). Such abilities have also been observed in monkeys with striate cortical ablation (*see* Pasik and Pasik, 1982, and Weiskrantz, 1986, for reviews). Up to now, however, it has not been shown whether the monkeys have 'blindsight' and, like the patients, do not possess a conscious representation of the stimuli presented within the field defect, or whether they have normal, albeit severely reduced (amblyopic) vision. Within their field defects, patients and monkeys may be able to detect and localize briefly presented targets (Pöppel *et al.*, 1973; Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1975, 1978; Mohler and Wurtz, 1977; Feinberg *et al.*, 1978; Stoerig *et al.*, 1985). They may have a measurable threshold to spatial and temporal modulation of a visual target (Weiskrantz *et al.*, 1974; Barbur *et al.*, 1980; Miller *et al.*, 1980; Blythe *et al.*, 1987), be able to discriminate the orientation of stationary lines (Weiskrantz *et al.*, 1974), detect that a target is moving (Weiskrantz, 1963, 1986; Magnussen and Mathiesen, 1989), and report its speed and direction (Barbur *et al.*, 1980; Blythe *et al.*, 1987). Eye

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movements in response to moving visual scenes have been reported (ter Braak and van Vliet, 1983; ter Braak *et al.*, 1971; Perenin *et al.*, 1980; Pizzamiglio *et al.*, 1984; Heide *et al.*, 1989), and the patients' reaction time to a target in the good field may be altered by the presentation of a second target in the blind half-field (Marzi *et al.*, 1986). Similarly, the perceived colour induced by a multicoloured array may be influenced by other colours presented in the blind field (Pöppel, 1986).

Although discrimination of triangles and squares (Schilder *et al.*, 1972; Weiskrantz *et al.*, 1974; Perenin, 1978) as well as of more complex patterns (Dineen and Keating, 1981) has been reported, discrimination of shape that is not based on the different orientation of the constituent contours (Weiskrantz, 1987) or on the natural variation in what Humphrey (1974) termed the salience or eye-catching property of some different shapes, may be absent (Blythe *et al.*, 1987). As is the case with form discrimination, in both human and nonhuman primates, evidence of wavelength discrimination in field defects is contradictory. Studying a destriated monkey, Humphrey (1974) found no evidence for discrimination of wavelength independent of physical intensity. By varying the suprathreshold reflectance of one of two simultaneously presented red and green stimuli it was always possible to find an equivalence point at which the two colours were indistinguishable to the animal. This equivalence point 'fell, in fact, closer to a scotopic than a photopic brightness match' (p. 250), implying that adaptation level no longer influences the shape or peak position of the sensitivity curve. This possibility was also investigated in macaque monkeys by Malmo (1966) and Leporé *et al.* (1975), who reported that after total or nearly total removal of the striate cortex, spectral sensitivity, previously very different under scotopic and photopic conditions, was now rod-like under both. As rod vision is colour blind this implied that genuine wavelength discrimination is absent in blindsight.

In contrast to these negative results are several reports demonstrating successful wavelength discrimination in field defects. Schilder *et al.* (1972, elaborated by Pasik and Pasik, 1982), reported that destriated monkeys could discriminate between red and green targets despite large variations in their intensity. Keating (1979) demonstrated discrimination between blue and yellow, and subsequently between blue and green, again despite variation in the intensity of both stimuli. Although neither study unequivocally demonstrates discrimination based solely on wavelength, chiefly because of the difficulty in matching spectral efficiency and image sharpness when spectral sensitivity and chromatic aberration could not be precisely controlled; in particular, blue-yellow and blue-green discriminations are not easily understood in terms of pure rod vision. Indeed, Humphrey's results, already mentioned as indicating no genuine wavelength discrimination, are puzzlingly equivocal. When tested with the same red and green stimuli on a red instead of a white photopic background the red/green equivalence point of the destriated monkey was now appropriate for photopic adaptation.

Bender and Krieger (1951) reported 'appreciation of colour' in several cortically blind patients as long as the stimuli were intense and prolonged. Barbur *et al.* (1980) measured a patient's spectral sensitivity under dark adaptation and found it to be normal for the adaptation level. The results of Perenin *et al.* (1980), who investigated residual colour processing in a patient with a complete bilateral field defect, are difficult to evaluate. The patient was able to identify a number of large coloured stimuli during the first examination, but was unable to discriminate their colour subsequently. Blythe *et al.* (1987) reported that 1 out of 25 patients with dense field defects could discriminate between monochromatic red (645 nm) and green (530 nm) lights, even though no forced-choice procedure was applied. Using such a procedure, Stoerig (1987) found that 6 out of 10 patients could discriminate red from green stimuli. As both targets were also detectable by forced guessing at an intensity of less than 1 log unit above low photopic background, these findings are not indicative of rod vision with its massively reduced sensitivity to long wavelengths. Regarding spectral sensitivity and wavelength discrimination in field defects there is unanimity on only one point: under dark adaptation spectral sensitivity is scotopic in man (Barbur *et al.*, 1980) and monkey (Klüver, 1941; Leporé *et al.*, 1975), indicating functional rod pathways from the retinal area that correspond topographically to the cortical lesion.

In view of these divergent results, we measured spectral sensitivity in 3 patients with blindsight, comparing measurements made under light and dark adaptation. We wanted to know whether spectral sensitivity is characteristic of rod absorption under both adaptation conditions, that is, whether the Purkinje shift is absent, indicating loss of cone activity. Should the Purkinje shift be present under light-adaptation, the photopic spectral sensitivity could reflect either the sensitivity of the luminance system with its single broad peak around 555 nm (King-Smith and Carden, 1976) or, alternatively, the sensitivity of the colour-opponent system with its multiple maxima at approximately 450, 550 and 600 nm (Sperling and Harwerth, 1971). Examples of these three types of increment-threshold spectral sensitivity curves, measured at 10° and 30° eccentricity on the 135° meridian in the temporal hemifield of control subject C2, are given in fig. 1. One was measured under dark adaptation (0.0001 cd/m^2 background, 116′, 200 ms stimuli), the other two under light-adaptation. To favour the colour-opponent system, the 116′, 200 ms stimuli were presented at 10° eccentricity on a white background of 32 cd/m^2. To favour the luminance system, the third curve was measured at 30° eccentricity on the same meridian with a 44′, 200 ms stimulus flickering at 5 Hz. Although a faster flicker rate may seem more appropriate for the luminance system's high temporal resolution, we used 5 Hz because under the present conditions the critical flicker fusion threshold for the 450 nm stimulus was only about 7 Hz. No background was used, and the colours of the small flickering targets were not identifiable at threshold. The curves are in good general agreement with the data of King-Smith and Carden (1976), and the standard Commission Internationale de l'Eclairage (CIE) scotopic luminosity curve.

As the retinal ganglion cell layer degenerates transneuronally after a striate cortical lesion in macaque monkeys (Van Buren, 1963*a*; Cowey, 1974; Dineen *et al.*, 1982) and man (Van Buren, 1963*b*), losing 50–80% of its colour-opponent Pβ ganglion cells (Cowey *et al.*, 1989; Weller and Kaas, 1989), it was particularly interesting to see whether colour-opponent processes can be demonstrated in the field defect. We therefore used conditions that favour the colour-opponent system, that is, a relatively large stimulus of 116′, a long presentation time of 200 ms, and a white adapting background (Sperling and Harwerth, 1971; King-Smith and Carden, 1976; Mullen, 1987; Snelgar *et al.*, 1987). Although we could only use a low photopic background luminance in addition to the scotopic one, the difference in sensitivity of the luminance and colour-opponent systems (King-Smith and Carden, 1976) should be sufficiently pronounced to allow attribution

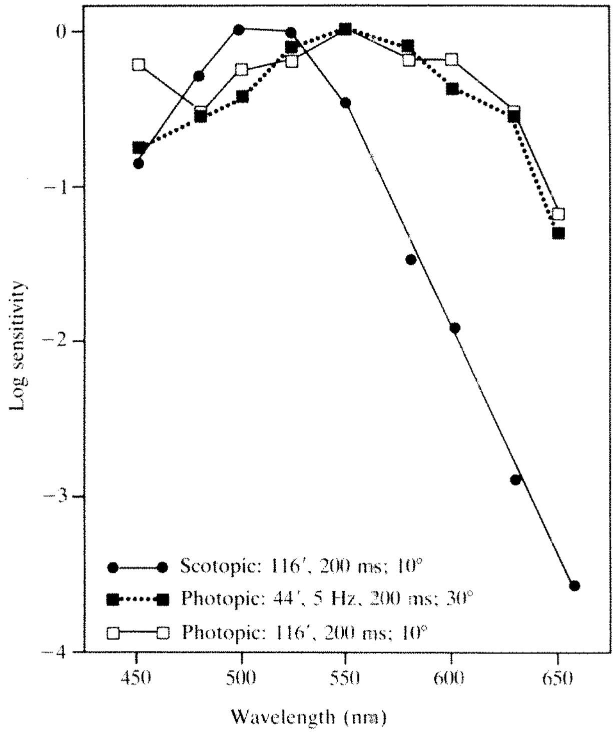

FIG. 1. Spectral sensitivity for a 116′, 200 ms spot measured at 10° eccentricity on the 135° meridian in C2's temporal hemifield when dark-adapted (background 0.0001 cd/m^2) and light-adapted (white background of 32 cd/m^2 luminance) to yield scotopic and colour-opponent photopic curves. In addition, under light-adaptation, at 30° eccentricity on the same meridian, spectral sensitivity was measured with a flickering 44′, 200 ms target to stimulate the luminance system preferentially. The curves are scaled to unity for easier comparison, and are in good agreement with data from other groups (e.g., Sperling and Harwerth, 1971; King-Smith and Carden, 1976; Snelgar *et al.*, 1987). *See* Methods for description of increment threshold measurements.

of photopic sensitivity in blindsight to one or other system, or to their combined action, or, should it resemble scotopic sensitivity, to the rod pathways. A brief report of part of this work has been published (Stoerig and Cowey, 1989*a*).

PATIENTS AND METHODS

Patients

Three patients, P1, P2 and P3, and 2 normally sighted, approximately age-matched control subjects, participated. The patients had suffered vascular incidents in the territory of the posterior cerebral artery that left them with homonymous visual field defects. Hypodense areas revealed by computer tomography (P1, P3) or nuclear magnetic resonance (P2) involved the optic radiations as well as the visual cortex in all patients. The least damage to white matter was seen in the scans of P2. P1 and P3 suffered marked initial memory deficits and P1 also had visual disorientation. P1 and P3 were male, born in 1915 and 1939, and suffered their lesions in 1982 and 1983, respectively. P2 was female, born in 1957, and suffered two vascular incidents. The first, which occurred in 1977, caused a quadrantanopic field defect which regressed spontaneously, and had completely disappeared when the second incident happened in 1984.

It reinstated the quadrantanopic which has since been stable. All 3 patients had previously participated in experiments on their residual visual functions (*see* Stoerig, 1987; Stoerig and Cowey, 1989*b*) and were highly trained observers. The 2 control subjects (C1, male, 53 y; C2, female, 36 y) had no history of ocular or neurological disease.

Visual field measurements

The visual fields of the patients were measured with a Tübinger perimeter (Sloan, 1971). The patients wore an eye-patch over one eye so that all tests of residual visual functions were carried out in the temporal visual field defect (nasal retina) of the other eye. With this eye—left in P1 and P2, right in P3—they fixated a central red fixation spot of 30′ diameter and a luminance of 20 cd/m^2. The homogeneous background was white, and had a luminance of 10 cd/m^2. A circular white stimulus of 116′ diameter and 320 cd/m^2 was moved slowly from the periphery towards the fixation point. The patients indicated when they first perceived it by pressing a buzzer. The exact position was marked, and the procedure was repeated along the other meridians at 15° intervals until the functional visual field was outlined.

In addition to the white stimulus, blue, green, and red stimuli (filters with peak transmission at 479, 550 and 632 nm, at maximum luminance; for details *see* Table 1) were used to map the parts of the visual field in which the patients could identify these colours. As before, the 116′ stimulus was moved slowly from the periphery towards the centre of the field. The patients' task in this case was not only to indicate the first appearance of the stimulus at the border of the functional visual field, but also to identify its colour as soon as they felt confident about it, the position being marked as before. The 3 coloured targets were given in a pseudorandom order, with yellow stimuli interspersed as catch trials, along 24 equally spaced meridians until the colour fields were outlined. The same measurements were made with the control subjects. The resulting plots all show that blue is perceived first; as usual, red and green fields are considerably smaller. The colour of the stimulus made no difference to the total size of the functional field.

In fig. 2 the fields measured with dynamic perimetry are combined with those from static perimetry, where the 320 cd/m^2 white stimulus appeared for 200 ms at a position within the field defect. The patient indicated by pressing a button whether or not he/she had perceived it. This procedure was repeated throughout the field defect as circumscribed by dynamic perimetry in order to delineate areas of incomplete functional loss. The peripheral portion of the quadrantanopic defect in P3 is amblyopic, his absolute defect having regressed in recent years. The resulting amblyopic portion is indicated by stippling. Although he reports stimuli that are flashed in this portion of his field, they rapidly fade and become invisible if presented for several seconds.

In addition to this procedure, incremental thresholds were measured along the meridians used for further testing. This was the 225° meridian for P1, 135° for P2, and 60° for P3. Measurements were extended into the functional visual field along the meridian mirror-symmetric with respect to the vertical meridian, i.e., 315° for P1, 45° for P2, and 120° for P3. An ascending method of limits was used. The stimulus was flashed for 200 ms at a given position on this meridian, and its luminance was increased in 0.05 log unit steps until the patients could just detect it. This procedure was repeated at intervals of 1° along the meridian indicated above. The resulting curves are given in fig. 3.

Measurement of spectral sensitivity

This is not straightforward and requires explanation. The great majority of measurements of spectral sensitivity under photopic conditions are carried out at suprathreshold levels and are actually measurements of spectral luminosity. The three major methods are (1) direct-comparison brightness matching of targets of different wavelengths, (2) the minimization of perceived flicker when 2 lights of different spectral composition are rapidly alternated, and (3) colour matching between a monochromatic target of variable intensity and an adjacent mixture of monochromatic lights of known energy. The advantage of these methods is that the perceptual judgement is determined by the summed response of all three classes of cone, even to a monochromatic target, because at the suprathreshold intensities used all wavelengths stimulate all cone types, albeit to different extents. The spectral luminosity function is therefore a smooth bell-shaped curve and sensitivity at each wavelength is usually expressed as a fraction of its value at the most effective wavelength. This fraction is Vλ.

Judgements of equivalent brightness of colour, or minimal flicker, have not been studied in patients with blindsight, and would be very difficult because the patients lack a conscious representation of the stimuli. Therefore a guessing procedure was used to measure the detection of a coloured target whose

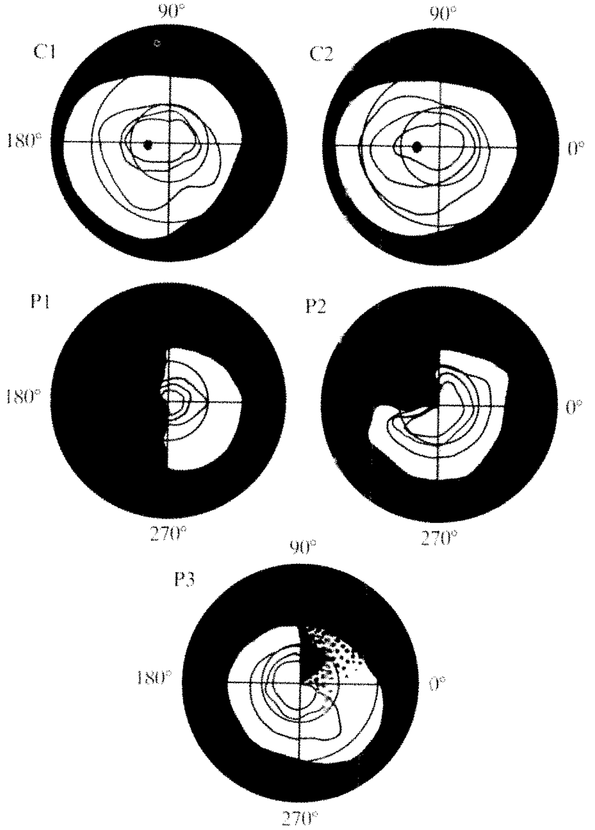

FIG. 2. The visual fields of the subjects determined with static and dynamic perimetry using white, blue, green, and red targets. The outermost border indicates the field for detection of a white target. The three following borders indicate, respectively, the outer edge of the region in which the subject could identify the colour of a blue, red or green stimulus moving slowly towards the fixation axis. Stimuli were 1 : 6, had maximum transmission at 479, 550, and 632 nm, and were presented at maximum intensity. The stippled area in P3 is amblyopic.

intensity is varied. At scotopic levels, this increment threshold method produces a smooth curve because only rods are effective, and whatever the wavelength of the stimulus it is perceived via the same receptors. At photopic levels, the class of cone providing the strongest signal at threshold varies with wavelength. The photopic spectral sensitivity curve measured in this way reflects the envelope of the individual sensitivities. Depending on the experimental conditions—the size of the stimulus, its duration, the luminance and wavelength of the background, the retinal eccentricity—it will resemble either the smooth curve representing sensitivity of the luminance system, or the bumpy curve with its various peaks and troughs reflecting the sensitivity of the colour-opponent system (*see* fig. 1).

In order to measure spectral sensitivity at threshold we presented 200 ms targets of different colour (*see below*, and Table 1) and determined the weakest stimulus that could be detected to a given criterion. The luminous intensity of the stimulus in photopic cd/m^2 (Pritchard photometer) was then taken from the calibration tables provided by the manufacturer of the perimeter (Oculus, Wetzlar, Germany). These photometric values already take account of Vλ, as reflected in the CIE photopic Vλ for the standard observer fixating a 2° target centred on the fovea. The threshold luminous intensities were therefore divided by the value of photopic Vλ for each peak wavelength in order to determine actual spectral efficiency. However,

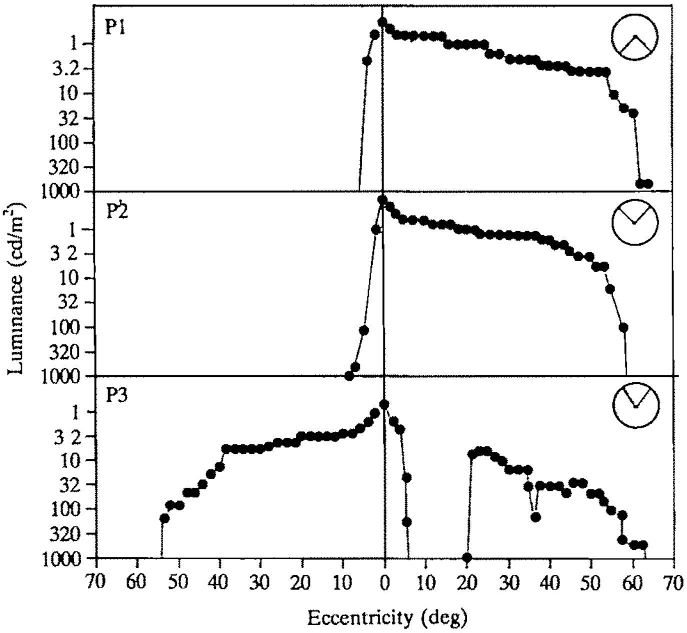

FIG. 3 Increment thresholds measured with a 116′ white target on a 10 cd/m^2 white background along the meridians used for testing spectral sensitivity, as indicated by the inserts at top right.

there are several possible problems with calculating radiance values in this way. Errors can arise if the peak wavelength of the stimulus is known only approximately (Verriest *et al.*, 1974). The most effective wavelength for a given filter may deviate from peak transmission if either the energy of the light source changes rapidly with wavelength, or where the Vλ function is steep, for example below 500 nm and above 525 nm for scotopic conditions. To assess these errors we convolved the transmissivity curves of the filters with (1) the energy-wavelength function of the light source, and (2) with photopic and scopotic Vλ. In all cases the transmission curves of the filters were so narrow (in relation to the curves for energy or Vλ) that the most effective wavelength remained the peak wavelength. However, there are two further points to consider. One concerns the yellowing of the lens with age, which progressively depresses sensitivity to short wavelengths after the age of about 30 y. The expected depression is about 0.1−0.15 log units in the 2 oldest subjects (Crawford, 1949). The second is that our measurements of threshold spectral sensitivity were made at eccentricities of from 10° to 30°, for which there are no standardized measures of Vλ. These two considerations may explain why our scotopic sensitivity curves are depressed by up to 0.4 log units at the 2 shortest wavelengths in comparison with the CIE scotopic curve (*see* figs 4, 5, 12). We therefore stress that our absolute values of sensitivity are much less important than the relative sensitivity of the intact and blind fields, for all possible sources of error apply equally to both.

Two adaptation levels were used: one scotopic at 0.0001 cd/m^2, the other photopic at 10 cd/m^2. Additional measurements were made at 32 cd/m^2. The background was white, from a source whose colour temperature, according to the manufacturer, was 3400° K. For measurements under scotopic conditions, the subjects were first dark-adapted for 20 min. The fixation spot was circular, red, and 30′ in diameter; its luminance was 0.2 or 20 cd/m^2 under dark and light adaptation, respectively. Fixation was monitored under both conditions by an infrared video-camera that viewed the eye through an aperture in the perimeter in the position of the natural blind spot and provided a magnified picture of the subject's eye on a monitor next to the experimenter. The subject's eye was 'illuminated' with an infrared light source attached to the head-bar.

TABLE 1 SPECIFICATIONS OF THE SCHOTT FILTERS USED TO PRODUCE THE COLOURED TARGETS

Filter no.	*Peak Transmission* *(nm)*	*at Halfwidth* *(nm)*	*Max. luminance* *(cd/m²)*
761903.4101	451	10	0.33
74810.12	479	12	5.34
82436.123	498	13	11.46
12084.49	526	11	27.7
75366 18	550	9	44.0
73464.1002	579	12	41.4
74865.1091	597	11	45.5
75673.390	632	11	20.4
75797.37	657	13	7.92

Stimuli

Stimulus size was 116′; presentation time was 200 ms throughout the experiments. Nine narrowband interference filters (Schott) were inserted into the projection beam of the perimeter. Filters are specified in Table 1. Of the 9 stimulus colours, 2 appeared blue, 3 green, 1 yellow, 1 orange and 2 red.

Threshold measurements in the functional visual field

As the same eye was used to measure detection in the blind and in the functional half-field, data from the functional half-field are always from the nasal half-field. In both half-fields a 10° eccentric position was tested in all subjects. In P1, who was tested in the lower visual field, a 40° eccentric position was also tested. The extent of the upper half-field is variable between subjects, and in P2 and P3, one 30° (P3) and one 40° (P2) eccentric position was used in addition to the 10° eccentric one. Positions in the functional field was symmetric, with respect to the vertical meridian, to those tested in the blind field.

The control subjects were tested at 10° and 40° (C1) or 10° and 30° (C2) eccentric positions in both nasal and temporal hemifield. In C1 the lower (225° and 315°), in C2 the upper oblique meridians (45° and 135°) were chosen. Test positions are summarized in Table 2.

TABLE 2 POSITIONS AT WHICH INCREMENT-THRESHOLD SPECTRAL SENSITIVITY WAS DETERMINED*

	Position (eccentricity/meridian)				
Case	*P1*	*P2*	*P3*	*C1*	*C2*
Temporal (blind) hemifield	10/225° 40/225°	10/135° 40/135°	10/60° 30/60°	10/225° 40/225°	10/135° 30/135°
Nasal (normal) hemifield	10/315° 40/315°	10/45° 40/45°	10/120° 30/120°	10/315° 40/315°	10/45° 30/45°

* In P1, P2, C1 and C2, the left eye was used. In P3, the right eye was used because his lesion was caused by a left hemisphere incident.

In every session, incremental thresholds were measured at these positions in the functional field, under either light or dark adaptation. Starting with a stimulus luminance that the subject could not detect, luminance was increased in 0.05 log unit steps until the subject reported just seeing the stimulus. Presentation rate was roughly 1 every 4 s. Every presentation coincided with a click from the perimeter shutter; the subjects responded after this click by saying 'yes' or 'no' according to whether or not they could detect the target. When the subject reported seeing the target on 3 consecutive presentations, its luminance was taken as incremental threshold. The procedure was repeated for each one of the 9 colour stimuli. As the duration of adaptation as well as the duration of testing influence sensitivity, these measurements were made at different points during the testing session, at the beginning, in between or at the end of the session. In part of the series, subjects were asked whether they could report the colour of the threshold stimulus, and the responses were noted.

The same procedure was adopted for measuring the incremental thresholds at 30° eccentricity in the amblyopic part of P3's field defect.

Threshold measurements in the blind visual field

In the blind visual field, targets were presented in pseudorandom order with blank trials. The sequence was predetermined for each session, and consisted of a mean of 4 blank trials per target presentation. This uneven ratio between targets and blanks was chosen because previously published detection data gathered in blind fields showed that detection is enhanced when the probability that a target will be presented differs markedly from the probability for blank trials (*see* Stoerig *et al.*, 1985; Stoerig and Pöppel, 1986). The patients were informed about this ratio (*see* Stoerig, 1987, for reasons). Both target and blank presentations were accompanied by the above-mentioned identical click; the patients responded by saying 'yes' or 'no'. As they could not see the targets, they had to guess whether or not a target had been presented. Ten demonstration trials, in which the patient was told whether or not a visual stimulus was present, were given before each 250-trial block.

To obtain threshold values for the blind field, this procedure began with targets 0.1 log units above threshold luminance as established for the corresponding position in the functional half-field. It was thereby assumed that thresholds in the blind field would not be lower than in the good field, although the temporal half-field is more sensitive than the nasal under normal conditions. After 100–250 presentations, target luminance was increased by 0.1 log units until detection became statistically significant. A minimum of 250 presentations was given with the threshold stimulus. The percentage of correct responses (p(0/0) and p(1/1)) was calculated together with the standard error that was derived from the binomial distribution. A χ^2 test was applied to determine statistical significance at the 5% level. To ensure that threshold readings were repeatable, or only varied within the usual fairly narrow range, several stimuli whose threshold luminance had been previously established were presented again in the same fashion, but either 0.1–0.2 log units above or below threshold luminance. If sensitivity was different on these control trials the mean luminance was used.

In the present paper we compare data gathered in the blind field with those from the normal and amblyopic fields. As a 'seeing' criterion was used in the normal and amblyopic fields and a 'guessing' criterion in the blind field, we compared these two different sensitivity measures at a position in the normal field of P2. At 10° eccentricity on the 45° meridian, we measured incremental thresholds first with the usual method of increasing luminance until she reported seeing the target. We then chose a luminance 0.3 log units below the threshold values and presented them in random order with blank trials. We asked her to guess whether or not a target had been presented. Stimulus luminance was increased as in the blind field until her detection became statistically significant. When this occurred she also reported seeing the target.

Control measurements

To exclude the possibility that statistically significant detection occurred when the stimuli were intense enough to provide detectable stray light in the functional visual field, the previously established threshold stimuli of each colour were presented in the same fashion on the natural blind spot of the same eye. These control measurements were made under light and dark adaptation. When 2 different luminance values had been found for the 2 positions tested in Cases P1 and P2 under light adaptation, the brighter one was used for the controls. The position of the blind spot was assumed to be mirror symmetric with respect to the vertical meridian, to that in the other eye; it could not be directly measured in any patient as it lay within or on the border of the field defect.

In addition, under light adaptation, the most intense stimuli that the perimeter can produce were presented on the blind spot to see whether a threshold for 'stray light detection' could be measured. Even the most intense stimuli with luminances greater than 40 cd/m^2 were not intense enough to produce significant detection in the blind spot. Under dark adaptation, where the range of possible contrasts encompasses several log units, stray light detection thresholds could be measured. The luminance of stimuli presented on the blind spot was increased until the subjects, who were asked to pay attention to a diffuse change in luminance, a halo, or any other change that might indicate the presence of a target, responded. Also under dark adaptation, the same procedure and instructions were followed at the 10° eccentric test positions within the field defects of P1 and P2 to see whether the reflectance of the retina, normally lower than that of the optic disc, was altered as a consequence of transneuronal retrograde degeneration.

Perception

The patients were often asked whether they could perceive anything when the blind field was tested. Throughout the experiments, which involved from 2 to 4 three-hour sessions per month for approximately 6 months, they consistently claimed that this was not the case and that they never saw or felt anything that was related to stimulus presentation. In contrast, when stray-light detection thresholds were measured under dark adaptation, a halo or headlight-at-night effect was seen.

RESULTS

Scotopic adaptation

Fig. 4 shows spectral sensitivity measured at scotopic levels with the control subjects. For each subject, results are shown for both the nasal and the temporal fields, at 10° and 40° eccentricity in the lower quadrants of C1 and at 10° and 30° eccentricity in the upper quadrants of C2. All curves show the characteristic peak in sensitivity at 500 nm, and a steep decline in sensitivity at the longer wavelengths. Sensitivity is often slightly higher in the temporal half-field and at the 10° positions.

The thresholds measured in the normal nasal fields of Cases P1 and P2 are given in fig. 5. They are essentially similar in shape and in absolute sensitivity to the curves

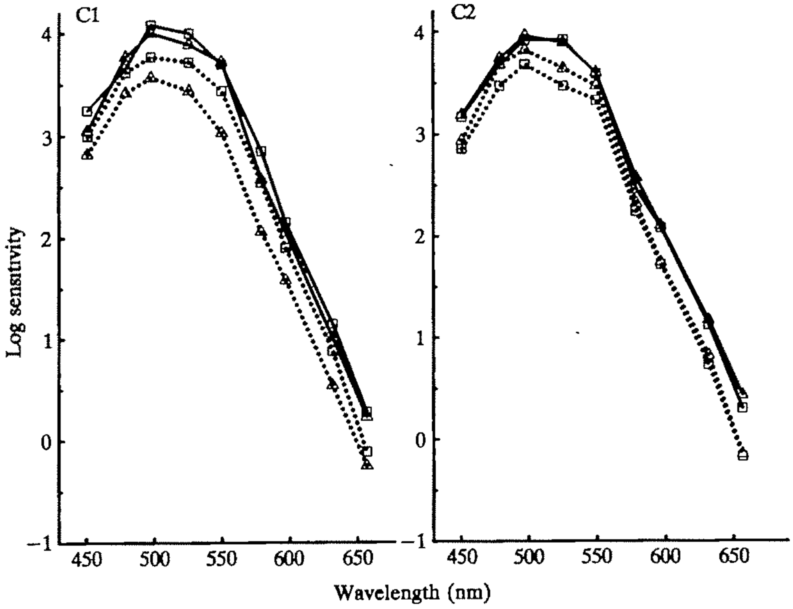

FIG. 4. Scotopic spectral sensitivity measured under dark adaptation on a background of 0.0001 cd/m^2 luminance in the control subjects Sensitivity is characteristic of the narrowly tuned rhodopsin absorption, with its maximum at 500 nm and a steep decline in the long wavelengths. As in the following figures, triangles and squares denote data from the nasal and temporal hemifield, respectively. Solid and dashed lines represent eccentricities of 10° or 30/40°, respectively.

for the nasal field positions of the control subjects. The thresholds measured with a guessing paradigm at 10° eccentricity in the blind hemifields are also plotted in fig. 5. They are characteristic of dark adaptation, with peak sensitivity at 500 or 525 nm. In comparison with the data from the symmetric position in the normal nasal half-field, overall sensitivity is reduced by up to 1 log unit. In terms of absolute sensitivity, the curves for the blind field resemble those for the more eccentric positions in the normal nasal field. They are less smooth than those from normal fields.

The percentage correct values that represent the patients' performance with the threshold stimuli are given in fig. 6. In all cases, performance with stimuli of a luminance 0.1 log units lower than threshold was not statistically significant.

Photopic adaptation

Thresholds for the control subjects under light-adaptation are given in fig. 7, again at 10° and 40° (C1) and 10° and 30° (C2) eccentricity. The curves show peaks at 450 and 550 nm, and a pronounced notch at 480 nm. Note that this notch and the accompanying peak of 450 nm indicating a contribution from the short wavelength cones, are absent from the curves measured at 30° eccentricity in C2. In no instance is there a steep decline in sensitivity at the long wavelengths.

A smaller notch at 580 nm (the Sloane-Crawford notch) is not obvious; at best a small shoulder is present. This is not unexpected in view of the fact that it is less evident in peripheral vision, and more conspicuous at higher adaptation levels (*see*, e.g., Snelgar *et al.*, 1987). We therefore made additional measurements at a 32 cd/m^2 background.

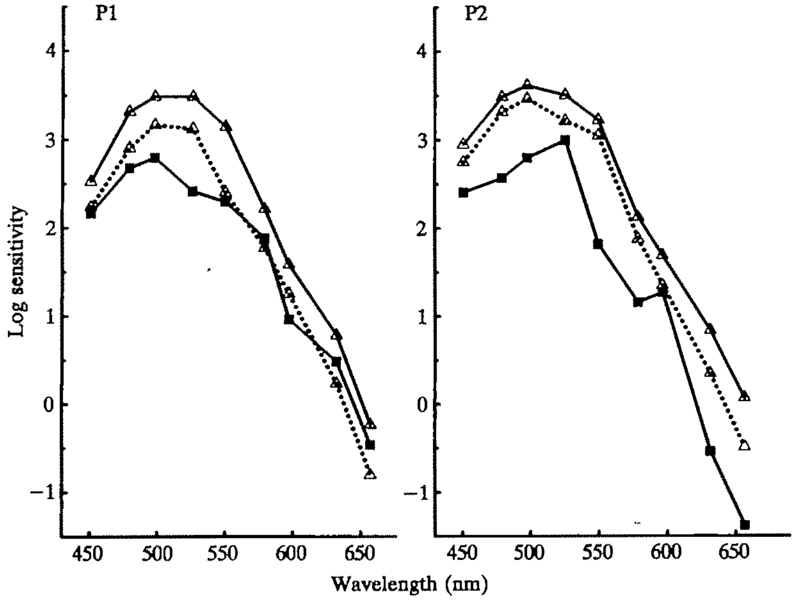

FIG. 5. Scotopic sensitivity of P1 and P2's normal nasal hemifields (open symbols) is no different from that of control subjects In the blind temporal field (closed symbols) it is reduced by up to 1 log unit. Albeit less smooth, the curves are essentially normal in shape. Solid line = 10°, dashed line = 40° eccentricity.

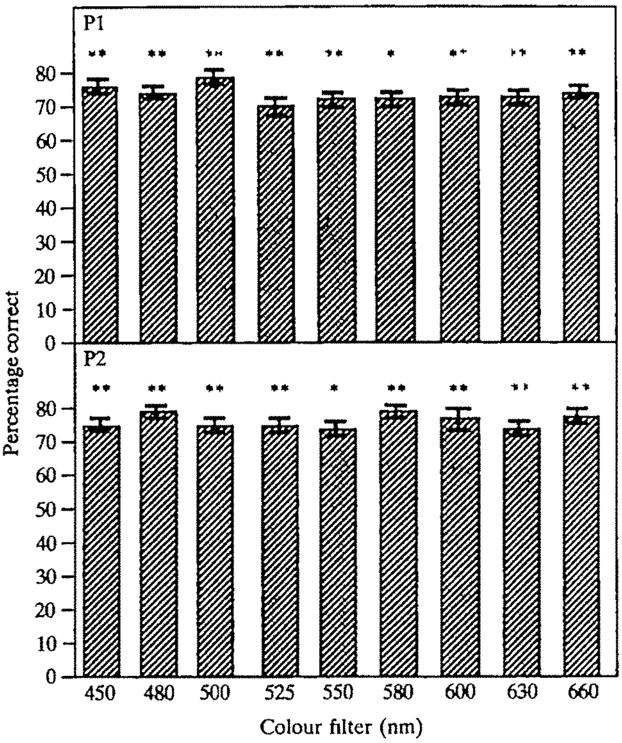

FIG. 6. The percentage correct values represent the patients' performance with the stimuli of threshold luminance as shown in fig. 5. The asterisks above the bars indicate the significance level: * $P < 0.05$; ** $P < 0.005$.

Although this comprises an increase in background luminance of only 0.5 log units it does enhance the notch at 580 nm in the temporal field of C1 and nasal field of C2, as shown in fig. 8.

The data from the patients are given in fig. 9. Again, the curves from the normal nasal field do not differ from those of the control subjects. Compared with the symmetric position in the normal nasal half-field, sensitivity in the blind field is reduced by up to a log unit. An exception is the curve representing measurements made at 40° in P1's normal nasal hemifield; at some points sensitivity at 40° in the blind temporal half-field appears to be higher than it does at 40° in the normal nasal half-field. The range of data for the nasal half-field position, however, was fairly large, straddling the curve for the normally more sensitive temporal field. As in the normal fields, the notch at 480 nm and peak at 450 nm are distinct. In all 3 patients, the curves are slightly uneven, making it difficult to identify peak sensitivity with certainty. However, it is certainly not at 500 nm, nor is there evidence of progressively decreasing sensitivity above 500 nm. The patients' performance with the stimuli of threshold luminance, at 10° eccentricity in the blind hemifield, as shown in fig. 9, is given as percentage correct values in fig. 10.

Like the control subjects, the patients were tested again at 10° eccentricity in both hemifields with the higher background of 32 cd/m^2 luminance to see whether peaks

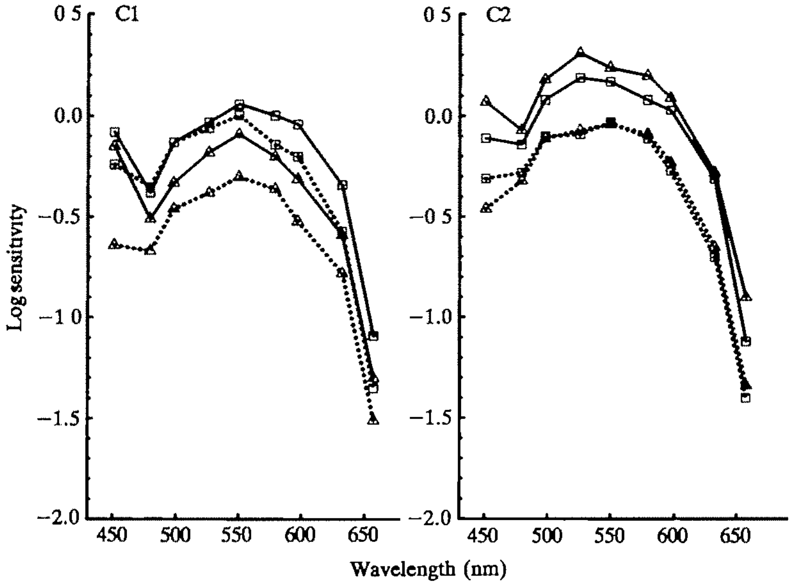

FIG. 7. Photopic spectral sensitivity measured on a 10 cd/m^2 white background in the control subjects. All curves, again measured at 10° and 40° (C1) and 10° and 30° eccentricity (C2) indicate cone activity. Those measured at 10° (solid lines), as well as the one measured at 40° in C1's temporal hemifield, show an increase in sensitivity from 480 to 450 nm that indicates a contribution from short wavelength cones. The peak at 450 nm is inconspicuous in the other curves from the 30° to 40° eccentric positions.

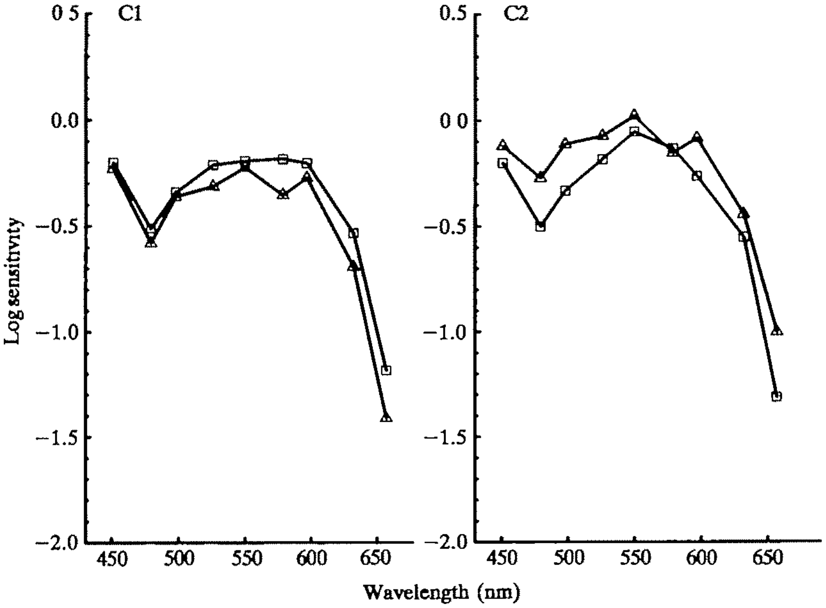

FIG 8 Photopic spectral sensitivity measured on a 32 cd/m^2 white background in the control subjects at 10° eccentric positions In addition to the notch at 480 nm, a smaller notch ('Sloan-Crawford notch') appears at 580 nm in two curves. Triangles = nasal, squares = temporal hemifield.

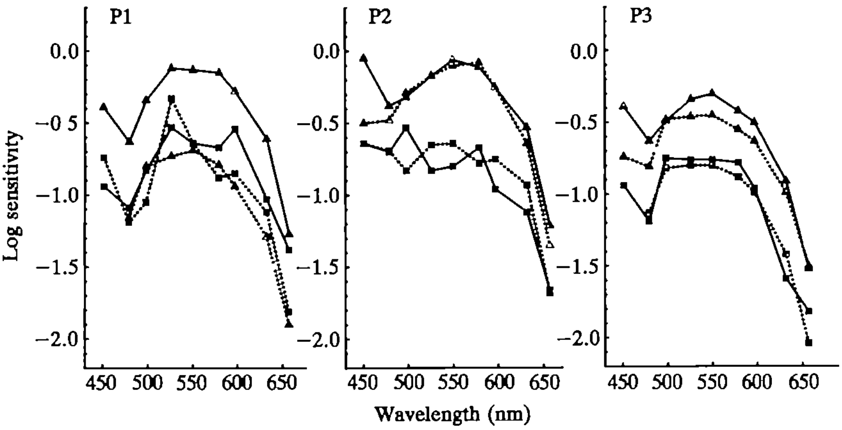

FIG. 9. Photopic spectral sensitivity measured on a 10 cd/m² white background in the patients. Curves for 10° eccentricity in either hemifield show an increase in sensitivity from 480 to 450 nm. For the curves measured more peripherally (dashed lines), this is also true for the temporal hemifields of P1 and P2 that normally have larger colour fields than their nasal counterparts. Curves from the peripheral positions in the normal nasal hemifields do not show this increase; indeed, in P1 and in P3's amblyopic field, the 450 nm stimulus was not detectable at maximum intensity.

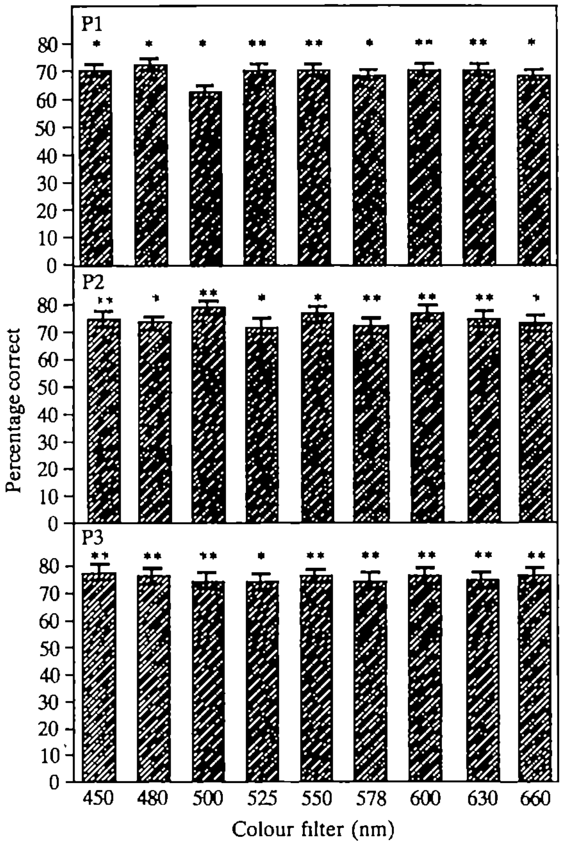

FIG. 10. The patients' performance of 10° eccentricity in their blind hemifields, with stimuli of threshold luminance as shown in fig. 8 Notation as in fig. 6

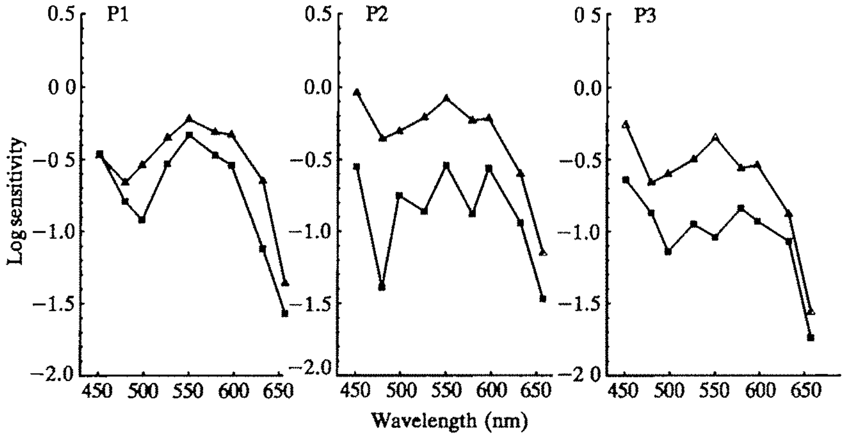

FIG. 11 The patients' spectral sensitivity measured at 10° eccentricity on a 32 cd/m² white background. Note that in addition to a notch at 480 nm, which was also present in the curves from the lower photopic background, a second notch at 580 nm appears in the curves from the normal hemifields. In the blind hemifields (filled squares) sensitivity is reduced.

and notches in the medium to long wavelengths would be clearer. As shown in fig. 11, this is indeed the case. All 3 curves from the normal hemifield show the Sloan-Crawford notch at 580 nm, with a flanking peak at both sides. In addition, the curves from the blind fields of both patients P1 and P2 also show peaks at 550 and 600 nm and a notch (P1) or a small shoulder (P2) at 580 nm in addition to the peak at 450 nm. In P3, sensitivity for the targets from 500 to 550 nm appears comparatively suppressed. Apart from this, the curves from the blind fields look normal for the adaptation level.

Throughout, the curves representing sensitivity in the field defects are less smooth than those for the normal field. However, the variance expressed in the bumps remains within the range of the data from the good field, and may well be due to the data points being based on 1−2 lengthy threshold measurements, as opposed to 3−9 for the normal field. Still, we cannot exclude the possibility that sensitivity in the blind field, especially in the medium wavelength part of the spectrum, displays larger fluctuations.

Purkinje shift?

The curves for light adaptation (10 cd/m²) and dark adaptation (0.0001 cd/m²) at the 10° eccentric positions are combined in fig. 12. To facilitate comparison of the light and dark-adapted curves the former are displaced vertically by the values shown in the legend.

It is obvious from fig. 12 that there is a clear Purkinje shift in the blind field in that dark-adapted sensitivity peaks at or close to 500 nm and declines steeply beyond 550 nm, whereas light-adapted sensitivity shows several peaks and no comparable decline at long wavelengths. The overall shape of the light-adapted curves indicates the activity of cones and opponent interactions between their outputs. The resulting percentage correct values for the dark-adapted condition are given in fig. 15. There was no evidence of significant detection under either condition.

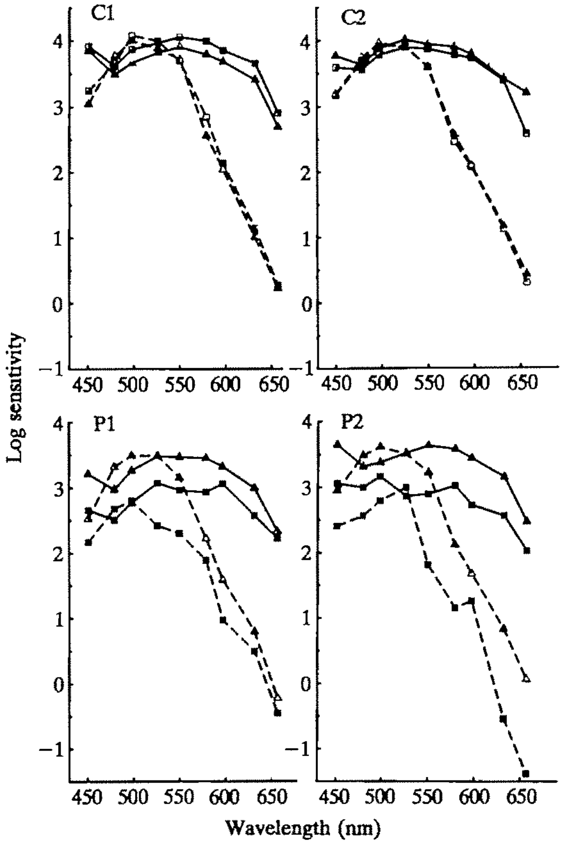

FIG. 12. In order to show the Purkinje shift, data gathered under dark (0.0001 cd/m^2) and light (10 cd/m^2) adaptation are combined. The light-adapted curves are raised vertically by 4.0 (C1), 3.6 (C2,P1) and 3.7 (P2) log units so that the horizontal separation of the dark and light-adapted peaks is clear (solid lines = light-adapted; dashed lines = dark-adapted)

Amblyopic field

In the course of several years of testing, the peripheral portion of P3's field defect slowly changed from scotomatous to amblyopic. In this portion, indicated by the stippled area in fig. 2, the patient can now detect flashed stimuli, but does not continue to see stimuli that are continuously present for several seconds. Even detection of flashed targets is unstable and may be abolished by repetitive presentations of a 200 ms stimulus.

Thresholds for the colour targets were measured at 30° eccentricity within this amblyopic field and 8 readings were taken for each target. The 450 nm target was not detectable at maximum luminance and the 660 nm target was detected in 4 trials. The curve in fig. 13 is based on the mean values of the available data, thus overestimating sensitivity for the 660 nm target, and resembles the sensitivity of the luminance system (*see* fig. 1). Unfortunately, the critical 450 nm point is absent, and remained unmeasurable even with binocular viewing. The range is about the same at the 30° positions in the normal and amblyopic half-field.

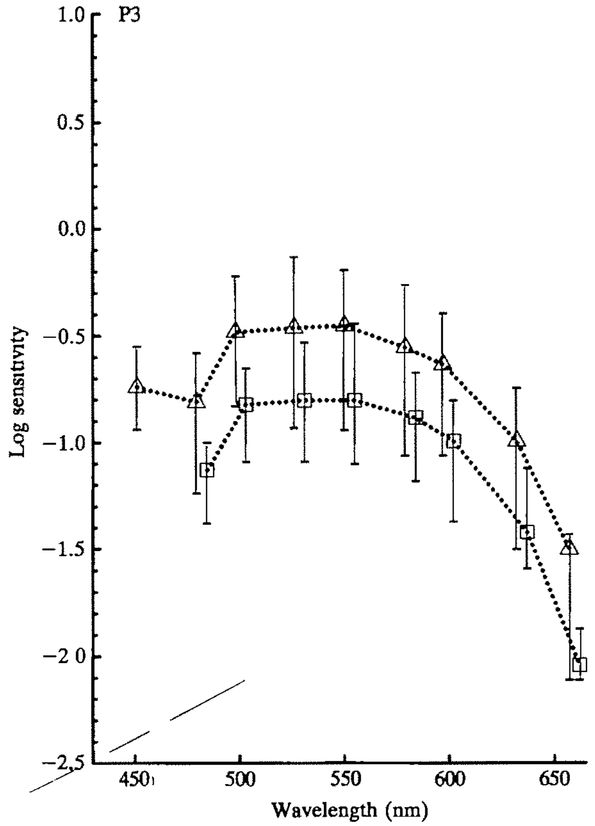

FIG 13. Spectral sensitivity at 30° eccentricity in P3's amblyopic temporal (squares) and normal nasal (triangles) half-field (range and means). At the amblyopic position, the patient could not detect the 450 nm stimulus at maximum intensity

Colour naming in the normal and amblyopic hemifield

At 10° eccentricity in the normal hemifield, under photopic conditions, colours could more often than not be correctly identified at threshold, that is, the luminance at which a stimulus was first detected on 3 consecutive trials. Most errors occurred at the medium wavelengths from 525 to 580 nm; none was observed with the blue and very few with the red stimuli. With the higher photopic background, identification was even better for all colours. Occasionally stimuli could be inconsistently detected at a slightly lower luminance. When this occurred, no colour was visible, with the exception of 2 blue stimuli. As soon as they were detected, they were also identified as blue. At the more eccentric positions, colour identification was poor, and even poorer in the nasal than in the temporal field. Here, consistently correct colour naming occurred with the blue stimuli only, and even this failed in the upper nasal hemifield of C2.

In his amblyopic field at 30° eccentricity P3 reported no perception of colour at threshold, nor did he report colours when the stimuli were presented at maximum intensities, that is, about 1.0 log units above his threshold. On the whole, his vision appears transient and colourless in the amblyopic field.

Control measurements

Seeing and guessing. For threshold estimation, a seeing paradigm was used in the normal field, and a guessing paradigm in the blind field. This might introduce a difference in threshold because the repetition stimulus presentation involved in the guessing method might elevate the threshold. Alternatively, being allowed to guess might shift the subject's criterion and yield lower thresholds. We therefore tried to estimate the influence of the paradigm on our measures of sensitivity by testing P2 at 10° eccentricity in her good field, using first the normal seeing paradigm, then, based on these results, the guessing paradigm (*cf.* Methods).

Fig. 14 shows the results of both sets of measurements. It can be seen that the difference is slight. Indeed, it is smaller than the fluctuations in thresholds seen when detection measurements are repeated in different sessions.

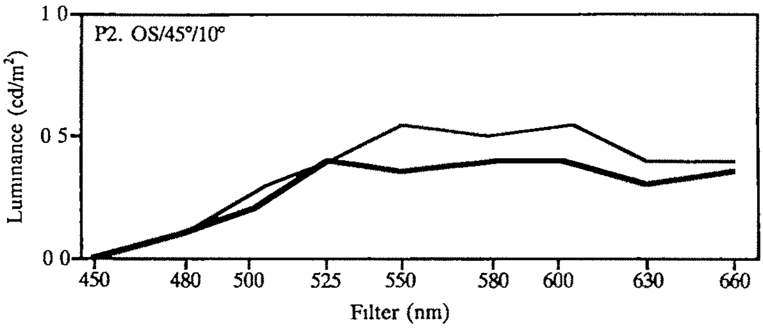

FIG. 14. P2's increment thresholds measured at 10° eccentricity in her normal hemifield with a 'seeing' (thick line) and a 'guessing' (thin line) paradigm. The difference is no more than 0.2 cd/m^2 throughout

Measurements in the blind spot. To ensure that the thresholds obtained for the blind field are not thresholds for detection of stray light scattered from the stimulus into the functional visual field, various control measurements were made. Under light and dark adaptation, the threshold stimuli were presented in pseudo random order with blanks on the natural blind spot of the patients, and detection was measured as in the blind field. Under photopic conditions, threshold stimuli had been determined for 2 retinal positions in the blind fields of P1 and P2. If the values for the 2 positions were different, the more intense stimulus of every colour was used. As the blind spot could not be directly measured in the patients due to its position within or on the border of the field defect, its position was assumed to be symmetrical to that of the blind spot measured in the other eye. The resulting percent correct values are given in fig. 15. There was no evidence of significant detection.

As it would be interesting to know the luminance at which stimuli would become detectable when presented on the blind spot, we tried to measure 'stray light detection thresholds'. Under photopic conditions, the most intense stimuli of every colour were presented on the blind spots of all subjects. Their luminance is shown in Table 1. In no case were they sufficiently intense to be detected by stray light.

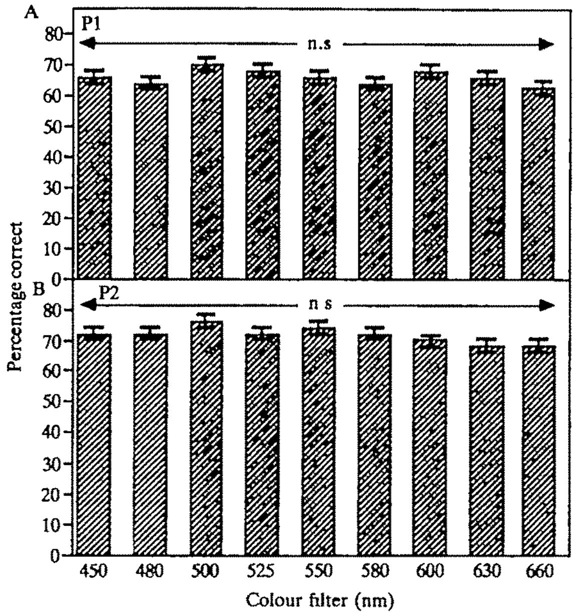

FIG. 15. The percentage correct values achieved by the patients when stimuli of threshold luminance as determined for the blind field positions were presented under otherwise identical conditions on the natural blind spot. In no case did performance reach a statistically significant level. A, B, dark-adaptation.

Under dark adaptation, where the stimuli of maximum luminance are several log units more intense than the background illumination, thresholds for detection on the blind spot could be measured with P1 and P2 and both control subjects. Stimuli were presented for 200 ms, and intensity was increased until the subjects detected them. Perceptually this consisted of a large halo of unidentifiable colour. The exception occurred with the 660 nm red stimulus, which appeared red and seemed to 'flow' from the approximate position of the blind spot towards the fixation point. Its threshold luminance was in the photopic range, explaining the sensation of colour in this case.

Spectral sensitivity for stray light emitted from a stimulus on the blind spot is given in fig. 16. Sensitivity shows the normal narrowly tuned dark-adapted shape but is lower by approximately 2–3 log units than for a stimulus presented at an eccentricity of 10° in the nasal retina. As sensitivity in the blind field is reduced by only 1 log unit or less, there is a substantial difference in sensitivity between positions in the blind field and on the blind spot. The one exception is P2's value at 660 nm where the two sensitivities are much more similar.

The otherwise large difference makes it unlikely that sensitivity in the patients' blind field is attributable to scattered light. It could be argued, however, that the retinal area corresponding to the postgeniculate lesion may be unusually reflective as a consequence of transneuronal retrograde degeneration. To test this the same procedure was used to determine stray light detection thresholds at the 10° eccentric positions within the field defects. As before, the patients were instructed to report any change that would indicate the presence of a light. The resultant curves, given in fig. 16, show that sensitivity for

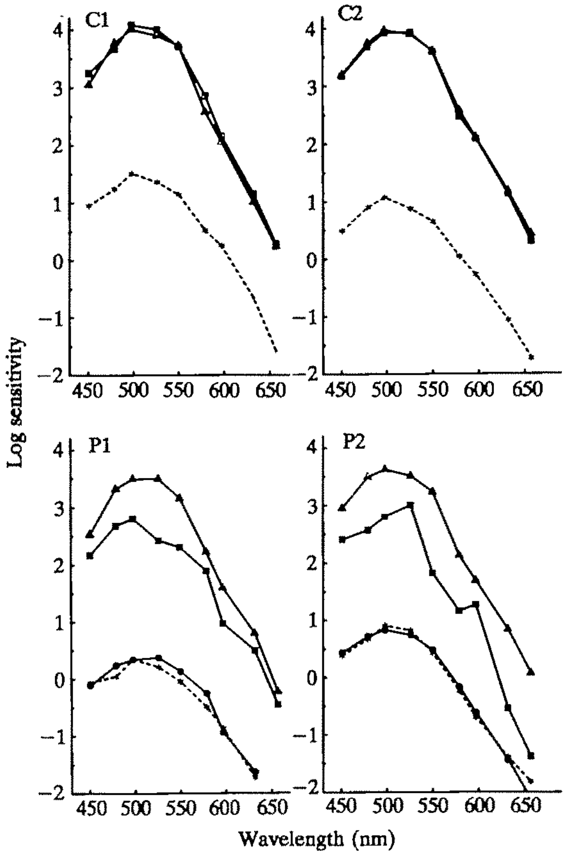

FIG. 16. Stray light detection thresholds measured under dark-adaptation with stimuli presented on the blind spot (dashed line) and at the 10° eccentric test positions in the field defects (closed circles) The patients' data show that sensitivity to stray light is similar at both positions, and by 2−3 log units lower than forced-choice guessing sensitivity in the blind field (squares), which it approaches at only one point (P2, 660 nm). Open symbols show sensitivity in intact fields.

stray light is similar in the blind spot and at 10° eccentricity in the field defect. This rules out the possibility that light scattered from the stimulus into the functional visual field is responsible for the much higher sensitivity of blindsight, although it remains possible that reflectance is higher than normal in the degenerated part of the retina.

DISCUSSION

Our results show that increment-threshold spectral sensitivity in the cortically blind visual field is as different at photopic and scotopic adaptation levels as it is in the normal field. Under dark adaptation it follows the smooth curve characteristic of rod vision, peaking at about 500 nm and declining steeply above 550 nm. Although the curves for the blind fields are less smooth than those for the intact field, they are otherwise normal, except that sensitivity is reduced by no more than 1 log unit. As sensitivity for detecting stray light, scattered from either the natural blind spot, or from the 10° eccentric test position within the field defect, is 2–4 log units lower than in the normal field, and approaches forced choiced guessing sensitivity in the blind field at only one point (P2, 660 nm), stray light artefacts can not explain the patients' statistically significant performance.

Under light adaptation, spectral sensitivity follows the shallow curve characteristic of cone vision. The curves that represent photopic sensitivity at 10° eccentric retinal positions have peaks at 450, 525–550 and, sometimes, at 580–600 nm. These peaks correspond to the sensitivity maxima of the colour-opponent system (Sperling and Harwerth, 1971; King-Smith and Carden, 1976; Snelgar *et al.*, 1987). In contrast, the luminance system, often equated with the broadband system, has but a single broad peak in sensitivity at about 555 nm, and sensitivity declines smoothly towards both longer and shorter wavelengths (King-Smith and Carden, 1976). Assuming that the most sensitive system determines threshold, it is likely that the luminance system contributes to sensitivity in the medium part of the spectrum where it is most sensitive, explaining the absence of a notch at 580 nm in several curves for normal and blind fields. Where the notch is present, it indicates inhibitory interaction between the medium and long wavelength cone inputs, implying a contribution from the red-green opponent channel. As expected, this is more pronounced at the higher photopic adaptation level (Snelgar *et al.*, 1987). Furthermore, the sensitivity of the luminance system decreases markedly in the short wavelengths, probably because the short wavelength cones (s or blue cones) provide little if any input to the broadband channel (Gouras, 1968; De Valois and Jacobs, 1968; Derrington *et al.*, 1984; Lee and Stromeyer, 1989). Therefore the first peak of 450 nm that is seen in all curves measured at 10° eccentricity indicates that threshold is predominantly determined by the blue-yellow colour-opponent channel.

These conclusions are in accordance with results from colour naming at threshold in the good field. The colour of the blue stimuli at 10° eccentricity could always be identified; mistakes were usually restricted to the medium range of the spectrum and were less frequent with the higher photopic background. At 30/40° eccentricity, colour naming was less reliable at all wavelengths, but still best for blue. In the curves from the 30/40° positions in the nasal half-field, no notch is seen at 580 nm, and the first peak at 450 nm is diminished, so that sensitivity begins to resemble that of the luminance system, presumably as the contribution of the broadband channel becomes relatively more effective. However, the insensitivity of the broadband channel to short wavelengths (*see above*) will still allow threshold detection of a blue target to be determined by a blue-yellow opponent channel even though its sensitivity also falls with retinal eccentricity. As colour fields are usually more extended in the temporal hemifield, it is not surprising that the curves from the blind temporal half-fields do indeed show an indication of the notches at 480 and 580 nm. Vision in the amblyopic field, however, appears to be dominated by the luminance system. Together, the curves from the eccentric positions provide evidence for a preponderance of broadband processing in the far periphery, which is also suggested by the results of Gouras (1968) and De Monasterio and Gouras (1975) on the distribution of functional cell types in the retina.

Our results show that both rods and cones are involved in the mediation of blindsight, and that some colour-opponent processing remains. As cone vision with more than one cone type is a prerequisite for wavelength discrimination, the results are consistent with reports of successful wavelength discrimination in the field defects of destriate monkeys (Schilder *et al.*, 1972; Keating, 1979; Pasik and Pasik, 1982) or patients with postgeniculate lesions (Bender and Krieger, 1951; Blythe *et al.*, 1987; Stoerig, 1987). However, wavelength discrimination thresholds may be dramatically increased, and this has yet to be tested. Broadband cells, which may have some weak opponency (Derrington *et al.*, 1984), are never completely unresponsive to the border between isoluminant hues (Lee *et al.*, 1989; Saito *et al.*, 1989), and respond poorly to short wavelengths (Gouras, 1968), could enable monkeys and patients to distinguish between short and long wavelengths. It is not clear how they could mediate discrimination between wavelengths in the medium to long range, or indeed anywhere in the spectrum when intensity is made irrelevant by varying it over a range that our present results show to be fully adequate.

What remains unsolved is the puzzling contrast between our results and others in which spectral sensitivity in totally destriated monkeys was scotopic and rod-like (Klüver, 1941) regardless of adaptation level (Humphrey, 1974; Malmo, 1966; Leporé *et al.*, 1975). One possible reason for the difference is that the extent of the field defect may be important. Our patients had defects that amounted to less than one-half of the visual field, whereas the monkeys had suffered total or almost total bilateral removal of striate cortex. This may influence adaptation level, which may be set by signals from the substantial functional part of the field. Total striate cortical ablation may also involve extrastriate cortical areas, and may interrupt projections from the thalamus to the extrastriate cortex. If so, monkeys with partial field defects should show the normal Purkinje shift and patients with total cortical blindness should not. The result of Perenin *et al.* (1980) are suggestive of the latter but are inconclusive as no attempt was made to determine the patient's spectral sensitivity. The 20 min period of dark adaptation used by Malmo (1966) and by Leporé *et al.* (1975), even before testing with targets of photopic luminance, may also have influenced the results. Lastly, suprathreshold measurements of spectral sensitivity produce different results from increment-threshold measurements. Whereas heterochromatic flicker photometry showed that peak spectral luminosity shifts from 550 to 560 at the fovea to 480 to 520 at 45° eccentricity (Abramov and Gordon, 1977; Weale, 1953), our results at 10° and 30°/40° eccentricity, under conditions favouring the colour-opponent system, show that sensitivity to the 450 nm blue stimulus *decreases* with eccentricity, revealing subtle changes which are in accordance with a decrease in the number of colour-opponent channels in the periphery, but no Purkinje shift. They are in good agreement with results of Wooten and Wald (1973) and Wooten *et al.* (1975) who reported that the sensitivity of the short wavelength cone mechanism was much lower in the far periphery than near the fovea.

In view of the massive retrograde transneuronal degeneration of retinal ganglion cells after striate cortical damage, the evidence for colour-opponent processes in the field defects is more surprising than the presence of a Purkinje shift. Although the cell types that degenerate in the human retina have never been studied (Van Buren, 1963*b*), the degeneration in monkeys is restricted to the Pβ cells (Cowey *et al.*, 1989) which provide the colour-opponent signals. At retinal positions corresponding to an eccentricity of 10° about 80% of the Pβ cells have degenerated 8 years after a unilateral striate cortical lesion in juvenile monkeys, a period comparable with that in the patients. However, Cases P1 and P3 both suffered their lesions at comparatively later stages in life than the monkeys, and the age at which the lesion occurs may influence the amount of degeneration (Dineen and Hendrickson, 1981; Weller and Kaas, 1989); later lesions produce considerably smaller cell loss. It is interesting to note in this context that both P1 and P3, whose lesions occurred when they were 67 and 44 years old, showed much clearer evidence for red-green discrimination in a previous experiment than P2, who suffered her first incident at 20 (Stoerig, 1987). As the cell loss also depends on retinal eccentricity, the surviving Pβ cells constituting 30% instead of 80% of the entire ganglion cell population at 10°, but still about 50% at 30–40° eccentricity in monkeys (Cowey *et al.*, 1989), relatively better wavelength processing may be expected at larger eccentricities. In addition, the Pα ganglion cells that provide the input into the broadband system do not show signs of retrograde degeneration. If the broadband system dominates photopic vision in the far periphery, it is not surprising that the curves measured at 30° or 40° eccentric positions in the blind field deviate even less from the normal curves than those measured at 10° eccentricity.

Greater depressions in photopic sensitivity, as measured at 10° eccentricity in the field defects, occur in the medium range of the spectrum. A selective depression of the luminance system, which we assume contributes to sensitivity under low photopic conditions in this part of the spectrum, could account for this, and is in accordance with previous findings under the same experimental conditions (Stoerig, 1987; Stoerig and Cowey, 1989*a*). It has recently been suggested, however, that the short/middle-to-long wavelengths colour system is phylogenetically older than the red/green one (Mollon, 1989), and a differential susceptibility of the two systems, suggested by Köllner (1912), may provide an alternative explanation for this depression.

Unless colour-opponent properties are created by opponent interactions between the ascending outputs of the spectrally biased cells of the superior colliculus (Kadoya *et al.*, 1971) in a manner that is not yet understood, the Pβ cells, being the only known retinal ganglion cells with clearly established wavelength opponency, must underlie colour-opponent processes in blindsight. In the latter case, our results imply that the remaining subpopulation of Pβ cells is functional. It follows that the surviving Pβ cells must have central projections, yet their only known normal target is the parvocellular portion of the LGN (Perry *et al.*, 1984) which degenerates rapidly and massively after postgeniculate damage (Van Buren, 1963*a*; Mihailović *et al.*, 1971). The geniculate neurons that project to extrastriate cortex (Bullier and Kennedy, 1983; Fries, 1981; Benevento and Yoshida, 1981) and which survive the degeneration (Yukie and Iwai, 1981) may therefore provide a functional retino-geniculo-extrastriate cortical pathway (Cowey and Stoerig, 1989), although they are probably not sufficiently numerous to sustain even the 100 000 or so Pβ cells that survive transneuronal degeneration in each hemiretina affected by complete unilateral striate cortical ablation in young monkeys. This indicates that other thalamic nuclei may receive input from these cells. However, it is not yet known which classes of ganglion cells in primates innervate thalamic nuclei such as the pulvinar that projects to extrastriate cortex and contains cells with colour-opponent receptive fields (Felsten *et al.*, 1983), or the perigeniculate nucleus which has multiple subcortical connections (Kaas and Huerta, 1988), extends its retinal projection area (Weller and Kaas, 1989) and, in baby monkeys, was reported to hypertrophy after striate cortical ablation (Dineen *et al.*, 1982).

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REFERENCES

Abramov I, Gordon J (1977) Color vision in the peripheral retina. I. Spectral sensitivity. *Journal of the Optical Society of America*, **67**, 195–202.

Barbur JL, Ruddock KH, Waterfield VA (1980) Human visual responses in the absence of the geniculo-calcarine projection. *Brain*, **103**, 905–928.

Bender MB, Krieger HP (1951) Visual function in perimetrically blind fields. *Archives of Neurology and Psychiatry, Chicago*, **65**, 72–79.

Benevento LA, Yoshida K (1981) The afferent and efferent organization of the lateral geniculo-prestriate pathways in the macaque monkey. *Journal of Comparative Neurology*, **203**, 455–474.

Blythe IM, Kennard C, Ruddock KH (1987) Residual vision in patients with retrogeniculate lesions of the visual pathways. *Brain*, **110**, 887–905.

Braak JWG ter, Vliet AGM van (1963) Subcortical optokinetic nystagmus in the monkey. *Psychiatria, Neurologia, Neurochirurgia*, **66**, 277–283.

Braak JWG ter, Schenk VWD, Vliet AGM van (1971) Visual reactions in a case of long-lasting cortical blindness. *Journal of Neurology, Neurosurgery and Psychiatry*, **34**, 140–147.

Bullier J, Kennedy H (1983) Projection of the lateral geniculate nucleus onto cortical area V2 in the macaque monkey. *Experimental Brain Research*, **53**, 168–172.

Cowey A (1974) Atrophy of retinal ganglion cells after removal of striate cortex in a rhesus monkey. *Perception*, **3**, 257–260.

Cowey A, Stoerig P (1989) Projection patterns of surviving neurons in the dorsal lateral geniculate nucleus following discrete lesions of striate cortex: implications for residual vision. *Experimental Brain Research*, **75**, 631–638.

Cowey A, Stoerig P, Perry VH (1989) Transneuronal retrograde degeneration of retinal ganglion cells after damage to striate cortex in macaque monkeys: selective loss of Pβ cells. *Neuroscience*, **29**, 65–80.

Crawford BH (1949) The scotopic visibility function. *Proceedings of the Physical Society, London, B*, **62**, 321–334.

De Monasterio FM, Gouras P (1975) Functional properties of ganglion cells of the rhesus monkey retina. *Journal of Physiology, London*, **251**, 167–195.

Derrington AM, Krauskopf J, Lennie P (1984) Chromatic mechanisms in lateral geniculate nucleus of macaque. *Journal of Physiology, London*, **357**, 241–265.

De Valois RL, Jacobs GH (1968) Primate color vision. *Science*, **162**, 533–540.

Dineen JT, Hendrickson AE (1981) Age-correlated differences of retinal degeneration after striate cortex lesions in monkeys. *Investigative Ophthalmology and Visual Science*, **21**, 749–752.

Dineen J, Keating EG (1981) The primate visual system after bilateral removal of striate cortex: survival of complex pattern vision. *Experimental Brain Research*, **41**, 338–345.

Dineen J, Hendrickson A, Keating EG (1982) Alterations of retinal inputs following striate cortex removal in adult monkey. *Experimental Brain Research*, **47**, 446–456.

Feinberg TE, Pasik T, Pasik P (1978) Extrageniculostriate vision in the monkey. VI. Visually guided accurate reaching behavior. *Brain Research, Amsterdam*, **152**, 422–428.

Felsten G, Benevento LA, Burman D (1983) Opponent color responses in macaque extrageniculate visual pathways: the lateral pulvinar. *Brain Research, Amsterdam*, **288**, 363–367.

Fries W (1981) The projection from the lateral geniculate nucleus to the prestriate cortex of the macaque monkey. *Proceedings of the Royal Society of London, B*, **213**, 73–80.

Gouras P (1968) Identification of cone mechanisms in monkey ganglion cells. *Journal of Physiology, London*, **199**, 533–547.

Heide W, Koenig E, Dichgans J (1989) Optokinetic nystagmus and visual-vestibular convergence in patients with large central scotomata. *Investigative Ophthalmology and Visual Science*, **30**, Supplement, 49.

HUMPHREY NK (1974) Vision in a monkey without striate cortex: a case study. *Perception*, **3**, 241–255.

KAAS JH, HUERTA MF (1988) The subcortical visual system of primates. In: *Neurosciences. Comparative Primate Biology*, Volume 4. Edited by H. D. Steklis and J. Erwin. New York: Alan Liss, pp. 327–391.

KADOYA S, WOLIN LE, MASSOPUST LC (1971) Collicular unit responses to monochromatic stimulation in squirrel monkey. *Brain Research, Amsterdam*, **32**, 251–254.

KEATING EG (1979) Rudimentary color vision in the monkey after removal of striate and preoccipital cortex. *Brain Research, Amsterdam*, **179**, 379–384.

KING-SMITH PE, CARDEN D (1976) Luminance and opponent-color contributions to visual detection and adaptation and to temporal and spatial integration. *Journal of the Optical Society of America*, **66**, 709–717.

KLÜVER H (1941) Visual functions after removal of the occipital lobes. *Journal of Psychology*, **11**, 23–45.

KÖLLNER H (1912) *Die Störungen des Farbensinnes: ihre Klinische Bedeutung und ihre Diagnose*. Berlin: S. Karger.

LEE BB, MARTIN PR, VALBERG A (1989) Nonlinear summation of M- and L-cone inputs to phasic retinal ganglion cells of the macaque. *Journal of Neuroscience*, **9**, 1433–1442.

LEE J, STROMEYER CF (1989) Contribution of human short-wave cones to luminance and motion detection. *Journal of Physiology, London*, **413**, 563–593.

LEPORÉ F, CARDU B, RASMUSSEN T, MALMO RB (1975) Rod and cone sensitivity in destriate monkeys. *Brain Research Amsterdam*, **93**, 203–221.

MAGNUSSEN S, MATHIESEN T (1989) Detection of moving and stationary gratings in the absence of striate cortex. *Neuropsychologia*, **27**, 725–728.

MALMO RB (1966) Effects of striate cortex ablation of intensity discrimination and spectral intensity distribution in the rhesus monkey. *Neuropsychologia*, **4**, 9–26.

MARZI CA, TASSINARI G, AGLIOTI S, LUTZEMBERGER L (1986) Spatial summation across the vertical meridian in hemianopics: a test of blindsight. *Neuropsychologia*, **24**, 749–758.

MIHAILOVIĆ LT, ČUPIĆ D, DEKLEVA N (1971) Changes in the numbers of neurons and glial cells in the lateral geniculate nucleus of the monkey during retrograde cell degeneration. *Journal of Comparative Neurology*, **142**, 223–229.

MILLER M, PASIK P, PASIK T (1980) Extrageniculostriate vision in the monkey. VII. Contrast sensitivity functions. *Journal of Neurophysiology*, **43**, 1510–1526.

MOHLER CW, WURTZ RH (1977) Role of striate cortex and superior colliculus in visual guidance of saccadic eye movements in monkeys. *Journal of Neurophysiology*, **40**, 74–94.

MOLLON JD (1989) 'Tho' she kneel'd in that place where they grew....' The uses and origins of primate colour vision. *Journal of Experimental Biology*, **146**, 21–38.

MULLEN KT (1987) Spatial influences on colour opponent contributions to pattern detection. *Vision Research*, **27**, 829–839.

PASIK P, PASIK T (1982) Visual functions in monkeys after total removal of visual cerebral cortex. *Contributions to Sensory Physiology*, **7**, 147–200.

PERENIN MT (1978) Visual function within the hemianopic field following early cerebral hemidecortication in man—II. Pattern discrimination. *Neuropsychologia*, **16**, 697–708.

PERENIN MT, JEANNEROD M (1975) Residual vision in cortically blind hemiphields. *Neuropsychologia*, **13**, 1–7.

PERENIN MT, JEANNEROD M (1978) Visual function within the hemianopic field following early cerebral hemidecortication in man—I. Spatial localization. *Neuropsychologia*, **16**, 1–13.

PERENIN MT, RUEL J, HÉCAEN H (1980) Residual visual capacities in a case of cortical blindness. *Cortex*, **16**, 605–612.

PERRY VH, OEHLER R, COWEY A (1984) Retinal ganglion cells that project to the dorsal lateral geniculate nucleus in the macaque monkey. *Neuroscience*, **12**, 1101–1123.

PIZZAMIGLIO L, ANTONUCCI G, FRANCIA A (1984) Response of the cortically blind hemifields to a moving visual scene. *Cortex*, **20**, 89–99.

PÖPPEL E (1986) Long-range colour-generating interactions across the retina. *Nature, London*, **320**, 523–525.

PÖPPEL E, HELD R, FROST D (1973) Residual visual function after brain wounds involving the central visual pathways in man. *Nature, London*, **243**, 295–296.

SAITO H, TANAKA K, ISONO H, YASUDA M, MIKAMI A (1989) Directionally selective response of cells in the middle temporal area (MT) of the macaque monkey to the movement of equiluminous opponent color stimuli. *Experimental Brain Research,* **75,** 1–14.

SANDERS MD, WARRINGTON EK, MARSHALL J, WEISKRANTZ L (1974) 'Blindsight': vision in a field defect. *Lancet,* **i,** 707–708.

SCHILDER P, PASIK P, PASIK T (1972) Extrageniculostriate vision in the monkey. III. Circle vs triangle and 'red vs green' discrimination. *Experimental Brain Research,* **14,** 436–448.

SLOAN LL (1971) The Tubinger perimeter of Harms and Aulhorn: recommended procedures and supplementary equipment. *Archives of Ophthalmology,* **86,** 612–622.

SNELGAR RS, FOSTER DH, SCASE MO (1987) Isolation of opponent-colour mechanisms at increment threshold. *Vision Research,* **27,** 1017–1027.

SPERLING HG, HARWERTH RS (1971) Red-green core interactions in the increment-threshold spectral sensitivity of primates. *Science,* **172,** 180–184.

STOERIG P (1987) Chromaticity and achromaticity: evidence for a functional differentiation in visual field defects. *Brain,* **110,** 869–886.

STOERIG P, HÜBNER M, PÖPPEL E (1985) Signal detection analysis of residual vision in a field defect due to a post-geniculate lesion. *Neuropsychologia,* **23,** 589–599.

STOERIG P, PÖPPEL E (1986) Eccentricity-dependent residual target detection in visual field defects. *Experimental Brain Research,* **64,** 469–475.

STOERIG P, COWEY A (1989*a*) Wavelength sensitivity in blindsight. *Nature, London,* **342,** 916–918.

STOERIG P, COWEY A (1989*b*) Residual target detection as a function of stimulus size. *Brain,* **112,** 1123–1139.

VAN BUREN JM (1963*a*) Trans-synaptic retrograde degeneration in the visual system of primates. *Journal of Neurology, Neurosurgery and Psychiatry,* **26,** 402–409.

VAN BUREN JM (1963*b*) *The Retinal Ganglion Cell Layer.* Springfield, IL: C. Thomas.

VERRIEST G, PADMOS P, GREVE EL (1974) Calibration of the Tübinger perimeter for colour perimetry. *Modern Problems in Ophthalmology,* **13,** 109–112.

WEALE RA (1953) Spectral sensitivity and wave-length discrimination of the peripheral retina. *Journal of Physiology, London,* **119,** 170–190.

WEISKRANTZ L (1963) Contour discrimination in a young monkey with striate cortex ablation. *Neuropsychologia,* **1,** 145–164.

WEISKRANTZ L (1986) *Blindsight: A Case Study and Implications.* Oxford: Clarendon Press.

WEISKRANTZ L (1987) Residual vision in a scotoma: a follow-up study of 'form' discrimination. *Brain,* **110,** 77–92.

WEISKRANTZ L, WARRINGTON EK, SANDERS MD, MARSHALL J (1974) Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain,* **97,** 709–728.

WELLER RE, KAAS JH (1989) Parameters affecting the loss of ganglion cells of the retina following ablations of striate cortex in primates. *Visual Neuroscience,* **3,** 327–349.

WOOTEN BR, WALD G (1973) Color-vision mechanisms in the peripheral retinas of normal and dichromatic observers. *Journal of General Physiology,* **61,** 125–145.

WOOTEN BR, FULD K, SPILLMANN L (1975) Photopic spectral sensitivity of the peripheral retina. *Journal of the Optical Society of America,* **65,** 334–342.

YUKIE M, IWAI E (1981) Direct projection from the dorsal lateral geniculate nucleus to the prestriate cortex in macaque monkeys. *Journal of Comparative Neurology,* **201,** 81–97.

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BOOK REVIEWS

Intracranial Vascular Malformations. Edited by Daniel E. Barrow. 1990. Pp. 250. Parkridge, IL: American Association of Neurological Surgeons. Price $80.00.

This multiauthor book is published by the American Association of Neurological Surgeons, edited by Daniel Barrow. It presents the current neurosurgical view on the management of intracranial vascular malformations. It is of note that this is a neurosurgical book with 13 of the 16 chapters written by neurosurgeons as first author. Of the remaining 3, 2 are by neuroradiologists and even the first chapter on classification of neuropathology is written by a neurosurgeon in conjunction with a neuropathologist.

The bulk of the chapters concern the management of arteriovenous malformations. They describe the natural history, radiological diagnosis, perioperative management and a number of sections on definitive management which include 4 chapters on surgery, a chapter on interventional neuroradiology and a chapter on radiosurgery.

For a neurosurgeon, the chapters on surgical technique are extremely interesting. The chapter on Management of Deep Supratentorial and Brain Stem Arteriovenous Malformations and the following chapter on Staged Embolization and Resection of Giant Intracranial Arteriovenous malformations are astonishing. They present the work of two units that specialize in the surgical resection of lesions that most of us would probably consider irremovable. Nevertheless, the results presented appear to be excellent and give cause for reflection on the management of one's own patients with difficult AVMs.

The chapter on radiosurgery presents the experience of four different methods of delivery of radiation, but with the emphasis on the experience of the stereotactic 'gamma knife'. There seems little doubt that stereotactic radiotherapy by this technique is the method of choice at present for deep lesions under 3 cm in diameter, although there is the risk of re-bleeding during the 2 year period while the radiation obliterates the malformation. This risk appears equal to the normal re-bleeding rate for these malformations. The other forms of treatment, including stereotactic Bragg peak therapy using proton beams and other particles, are assessed. As presented, there seems to be little advantage in these alternative treatments.

The chapter on Interventional Radiology is disappointing. It presents the results of a single unit's experience and does not give an overview of the technique as a whole. Furthermore the authors do not discuss the risk of postembolization recanalization of these lesions.

The remaining chapters deal with classification and management of cavernous and other venous malformations. These are much less common. Nevertheless, the chapter on management by Dr McCormick is one of the best in the book, presenting a very careful analysis of world literature and a balanced overview.

The final chapter by Professor Eugene Flamm is an excellent summary of the whole book with an emphasis on clinical decision making.

Because this is a book by neurosurgeons for neurosurgeons it cannot present an entirely unbalanced view. However, there is no doubt that it is an extremely valuable book which presents the dilemmas in the management of these patients as well as the exciting therapeutic possibilities that can be achieved with a dedicated approach.

MICHAEL POWELL

Textbook of Child Neurology. Fourth edition. By John H. Menkes. 1990. Pp. 832. Philadelphia: Lea and Febiger. Price £51.44.

There is a wide range of textbooks of Child Neurology available in the United States, and among these, Menkes' book, which first appeared in 1974, is a leader. It has been republished at 5 year intervals. Five years is a long time in this specialty. As the author states in his preface, despite the increasing complexity of knowledge, with advances which have transformed biology, and unified genetics, biochemistry and cell biology into a single discipline, these advances have not yet had as profound an effect on the clinical process as they have had on the neurosciences. Above all, magnetic resonance imaging has radically altered the diagnostic approach and, to a large extent, changed paediatric neurology into an outpatients' specialty. The author's task in this edition has been more difficult than in its predecessors, despite the assistance of other experts.

The format of this edition differs little from that of the last but, in response to many requests, an introductory chapter on the neurologic(al) examination and neurodiagnostic studies has been added. Menkes pays tribute to Paine and Oppé's *Neurological Examination of Children,* an Anglo-American enterprise published 25 years ago (and elsewhere in the text to Richmond Paine's clinical contributions), with the hope that this chapter will prove as valuable to readers as their books have been to him. Written with the paediatrician and general neurologist in mind, this chapter has achieved its aim. Child neurology is still, and probably always will be, a clinical discipline; the big guns of the new imaging, genetics and biochemistry should only be brought to bear on a problem when a full history and examination have allowed a clear idea of the diagnostic possibilities to emerge. With financial constraints added to the need to protect defenceless children from inappropriate invasive techniques, our responsibilities in this area have become heavier. It is a very personal book. Menkes cites his own experience and is not afraid to use the personal pronoun to describe what he does and what he has found helpful, rather than the somewhat autistic third person, which seems, strangely, to have become accepted as the 'scientific' mode.

For the 15 chapters Menkes has only 5 helpers. Two, Weil on Infections of the Nervous System, and Kinsbourne on Disorders of Mental Development, contribute their own chapters. Three others collaborate with him in 4 other chapters. British paediatric neurosurgical expertise is represented by Kenneth Till in 3 joint chapters, on Malformations of the CNS, Postnatal Trauma and Injuries by Physical Agents and Tumors of the Nervous System. Inevitably the author's special interests and experience influence the emphasis and space devoted to topics. Thus the initial chapter on Metabolic Diseases is the most comprehensive; with its 111 pages and 733 references it almost rivals 'Stanbury'. In the chapter on Diseases of the Motor Unit more clinical details might usefully have been given on myotonia congenita and myotonic dystrophy. There is a valuable discussion of recent advances in the genetics of Duchenne dystrophy and of dystrophin. The recommendation of bedrest in a darkened quiet room in the treatment of Sydenham's chorea is somewhat controversial, and may perhaps be a residue from the days when it showed a closer association with acute rheumatic fever than is often seen in the developed nations today.

The illustrations are profuse and generally excellent, though a picture of the naevus in the Sturge-Weber syndrome could usefully be added to the next edition. The CT, MRI and other images are reproduced well on the more expensive, thicker, glossy paper which the publishers have managed to use, while keeping the price to a reasonable level.

The book is a very good buy for all those involved with the neurological problems of childhood.

EDWARD BRETT

Subcortical Dementia. Edited by Jeffrey L. Cummings. 1990. Pp. 267. Oxford and New York: Oxford University Press. Price £35.00.

Drs Jeffrey Cummings and Frank Benson have played a major role in the description of the syndrome of subcortical dementia advanced in modern form by Dr Albert. They have been consistent key exponents of the notion that behavioural features of some conditions, such as progressive supranuclear palsy, Huntington's disease and Parkinson's disease, are specifically different from those of others, such as Alzheimer's disease, and that the differences are related to the site of the major pathology—subcortical or cortical. In the OUP book *Subcortical Dementia,* Dr Cummings, as editor, draws together comprehensive evidence in support of that concept. In individual authoritative chapters, the book provides overviews of the syndrome, including its history, the relevant neuroanatomy and neurochemistry, and its neuropsychological assessment; and, in the main body of the book, descriptions of individual disorders, including subcortical infarcts, AIDS, MS and depression. The book clearly succeeds in providing a comprehensive account of the syndrome.

One difficulty in the concept of subcortical dementia as a specific unitary syndrome is understanding whether it is based on anatomical principles or behavioural ones. This confusion has inhibited study of subcortical dementia as a specific syndrome in the past and I fear it has not been clarified in Dr Cummings' book. One senses the diligent search for common behavioural features based on disruption of common neuroanatomy or neurochemistry to define the syndrome. However, sometimes this goal displaces the alternative approach of study of the clear behavioural and pathological *differences* that exist between the subcortical dementias and which may tell us as much about brain-behaviour relationships and their clinical application, as further definition of a unitary syndrome. In some places, this approach leads the reader to confusion: is thalamic aphasia, or impaired naming in Behçet's syndrome, an acceptable part of subcortical dementia, even though language is supposedly spared in the syndrome? Can the motor disorder of MS be seriously compared with that of other subcortical dementias? In a few places there are also inconsistencies: for example, the conflicting data on digit span in Alzheimer's disease (pp. 72 and 80).

The chapters describing the behavioural features of all the individual disorders are, in general, well-written, balanced and useful to the clinician or experimentalist, particularly the sections on Huntington's disease, progressive supranuclear palsy, vascular disease and AIDS. Sometimes the selection of reference material is idiosyncratic and there are unfortunate omissions to the general discussion: for example, although the text is primarily concerned with subcortical dementia, I should like to see some mention of cortical Lewy body disease in Parkinson's disease, more detail of multisystem atrophies and perhaps a review of intermittent pressure hydrocephalus.

The book is well-presented and well-printed. Apart from a few notable examples, the chapters could benefit from more illustration, particularly where difficult concepts are being expounded The chapters on neuroanatomy and neurochemistry, in particular, are scholarly but would be very difficult to follow if one has little previous acquaintance with the subject. The chapter on neuroanatomy should be illustrated and both of these chapters would benefit from more functional analysis.

Dr Cummings has taken on the difficult task of presenting a relatively youthful and somewhat controversial syndrome primarily to a clinical audience. The resulting compendium includes material on the clinical features of specific conditions which is indeed useful to a behavioural neurologist. However, in unwrapping the features of the syndrome, and its pathological basis, he has produced a text that is perhaps more a valuable individualistic monograph to researchers in the field.

HARVEY J. SAGAR

Treatment of Chronic Pain. Possibilities, Limitations and Long-term Follow-up. Edited by M. Mumenthaler, P. A. Van Zwieten and J. M. Farcot. 1990. Pp. 337. New York: Harwood Academic Publishers. Price £95.00 hardback; $63.00 paperback.

This book is based on a meeting held in Strasbourg in 1989 that focused on problems encountered in treating chronic pain. This is an important and often neglected topic, doctors generally being more eager to extol the virtues and benefits of their therapeutic endeavours than to look at the failures and problems. Does the book succeed?

Certainly much material is presented, one suspects the authors' presentations being requested by the editors to provide a record of the meeting. The difficulty is that the coverage is so extensive, and ranges from the problem of steroids in the prevention of postherpetic neuralgia to a consideration of Schultz' autogenous training techniques, and from pituitary glycerol injection in cancer pain to a chapter on nerve injuries after conduction block (surely this title should have been rephrased?). One wonders, therefore, precisely for whom the book is intended. An attempt at cohesion is made by grouping the chapters together in sections, comprising headaches, therapeutics of painful peripheral neuropathy, minor analgesics and anti-inflammatory drugs, antidepressants, infiltrations and neural blockades, psychiatric and psychological support, neurostimulation techniques, surgical procedures (trigeminal lesions, DREZ lesions, cordotomy, pituitary neuroadenolysis), and morphine therapy (oral and parenteral, spinal and ventricular morphine, and narcotic intolerance).

Unless the whole book is read for an overview of these subjects, it is probably most useful as a book of reference The sheer mass of issues means few people are likely to be interested in all the topics, though probably all who work in the field would learn much of interest and importance. For example, there are interesting discussions on pitfalls and errors in the treatment of both acute migraine attacks and prophylactic therapy, time-dependent rhythms in inflammation and nonsteroidal anti-inflammatory drug kinetics, complications of sympathetic blockade (including the sanguine comment 'Neurolysis and litigation are potential bedfellows and we have to take account of this'), and problems of percutaneous cordotomy. The contribution on postsympathectomy pain is particularly interesting, not least for its historical perspective, and there is a very thoughtful chapter on the application of the biopsychosocial model to chronic pain, in which are indicated the limitations of the mechanistic approach to chronic pain, when psychosocial issues are ignored. Perhaps the oddest reflection on society reported in this book is that in the Federal Republic of Germany there are more than 500 drugs containing lithium on the market—so the chapters dealing with lithium side-effects seem entirely appropriate.

In conclusion, this is an interesting and valuable book, and with its 38 chapters from 36 contributors, it is most useful as a source of reference. It is unfortunate that there are spelling errors, curious sentence constructions, and even duplicated sentences. The book would have been very greatly improved and made easier to read if the editors or publisher had had the text corrected by someone whose first language was English.

G. D. SCHOTT

Brain Edema: Pathogenesis, Imaging and Therapy. *Advances in Neurology,* Volume 52. Edited by Donlin M. Long. 1990. Pp. 624. New York: Raven Press. Price $154.00.

While most neurologists have cause to consult this excellent series for clinical information, the volume reviewed here is not a text intended for the practising clinician. It is a reference text for researchers in the field of brain oedema, and the introduction promises a *broad* overview of *current* research. The book is physically robust and clearly printed, but rather heavy for the MD student to carry on his or her bike. The last 22 pages contain short, unreferenced abstracts which add little to the book except more weight. The meat of the text is a series of referenced papers in no particular subject order. It would have been better if the editor had attempted to organize the book into the categories mentioned in the title. Wishing to feel on home ground, I looked first at the papers on MRI. As I turned the pages, I was struck by the impression I had seen it all before. Although published in 1990, none of these papers contained a reference beyond 1987, and most were much earlier. Clasen's chapter on the principles of MRI is excellent but hardly relevant to the theme of the book. These papers add little to the work of the last 4 years which goes unmentioned. No space is given, for example, to the important advances in the use of contrast agents such as Gd-DTPA to quantify blood-brain barrier damage and oedema spaces, or diffusion imaging. This impression of déjà vu is continued throughout the book; the cortical freezing lesion is done to death yet again, and there are numerous papers on the use of osmotic agents and steroids. There are, of course, some interesting contributions too, such as the investigation of cerebral protection during reperfusion by Pereira *et al.* Overall, however, the promise of the Introduction is unfulfilled, and as an addition to the *Advances in Neurology* series, it describes few real advances and is not especially neurological. No doubt this book will find its way onto the shelves of avid collectors of the series and specialist libraries. I presume the absence of recent material is because the contributions were submitted in 1988, but anyone seeking current research on brain oedema would do better to sit at the keyboard of a computerized literature search facility for 20 minutes.

DAVID BARNES

Three Dimensional Neuroimaging. Edited by A. W. Toga. 1990. Pp. 317. New York: Raven Press. No Price.

This book is a little misleadingly titled in that the three-dimensional neuroimaging presented is specifically aimed at autoradiography, although some individual chapters are also applicable to tomographic data aquisition, that is, CT, MRI, SPECT, and PET. The volume is divided into 3 main sections: instrumentation and procedure, applications of neuroimaging, and a miscellaneous section. The first section describes methods of acquiring and displaying images, and details the computer hardware required for their display. A comparison of the various means of transforming and processing images, and of image edge detection is presented. Chapter 2 comprises a catalogue of the various sources of systemic and random errors that can arise during autoradiographic image acquisition and display. In chapter 4 problems specific to the 3D imaging of neuronal arborization are considered.

Section 2 contains chapters on the theory and practice of autoradiographic analysis of receptor density and binding affinity, and on approaches for producing 3D reconstructions from 2D autoradiographs of brain structure and function and relating these 3D reconstructions to a digitized 3D brain atlas. The final miscellaneous section discusses the problems that can arise in realigning contiguous tissue sections in order to produce a 3D reconstruction, and the use of warping techniques for correcting the distortion that can arise from tissue sectioning. The various approaches for generating surfaces in 3D neuroimaging are compared, and a semiautomated nerve tracing software package (CARTOS) is presented. In the final chapter the ideal database of brain information is discussed, and a current commercially-available database for rat bran, 'brainbrowser', is reviewed.

This volume has been compiled by a group of North American experts on 3D neuroimaging. It is well written and presented, and the computer graphics are beautifully illustrated. My chief problem is in trying to identify its main audience. The foreword suggests that students, clinicians, and researchers will all find this compilation of interest. I would doubt whether clinicians would find this work of immediate relevance, and the neuroscientists who would find it of interest would almost certainly need to have a basic knowledge of computer programming and of 3D algorithms for reconstructing biological material. Most of the thousands of biologists processing autoradiographic sections every day will be fascinated by the possibilties of 3D reconstruction presented by this book but are unlikely ever to possess the hardware or software for carrying out this type of data processing. They are also unlikely to be able to spend the time required to produce 3D reconstructions of their 2D sections. My overall impression is that while this is a beautifully presented and illustrated work, the audience will be limited and it will only have an impact on the small numbers of neuroscientists with access to gigabytes of computer power. I wonder whether a more general volume which also included tomographic neuroimaging might not have generated a wider audience.

David Brooks

Essentials of Neuroimaging. By J. R. Kirkwood. 1990. Pp. 497. Boston, MA and London: Little, Brown. Distributed by Churchill Livingstone. Price £65.00.

This text deals essentially with principles of neurodiagnosis, laying emphasis on those imaging features which reflect the anatomy and pathophysiology important in the differential diagnosis of the commoner disease processes: by doing so it provides the background information necessary for the categorization of most conditions that involve the nervous system.

The book was written for radiologists in training but it is equally suitable for clinicians. It commences with a short review of techniques, principally discussing their individual advantages and the anatomical features demonstrated. Normal anatomical features are discussed and illustrated with an admirable exclusion of potentially confusing and unimportant details. The dominantly used modalities of MRI, CT and angiography are emphasized in this and subsequent chapters with frequent comparisons of CT and MRI in the same patient, but the lesser used modalities are also adequately discussed.

The remainder of the book is traditionally arranged under headings dealing with the various pathological processes. Each chapter is clinically orientated with a sensible emphasis on the use of imaging in the diagnosis and management of the commonly encountered conditions. There are a large number of well selected illustrations with detailed captions indicating important positive features which are always clearly evident. Nearly all the images are of excellent quality: good use is made of tables which should prove particularly useful for examination candidates. There is a good index and each section ends with well selected suggestions for further reading.

It is of course always possible to pick out weaknesses in a text of this type in which simplification and generalization have to be carried close to the point of error. One should perhaps comment, for example, on the poor classification of spinal arteriovenous shunts from which the commonest of these, the dural arteriovenous fistula, is excluded. Perhaps also the student is encouraged to use contrast enhancement to a greater extent than is strictly necessary though it could equally be argued that for doctors at the level of expertise at which this text is directed the emphasis should be on acquiring as much information as possible to avoid errors in diagnosis.

Any trainee radiologist or clinician who absorbs the contents of this book will gain an excellent understanding of the principles of neuroradiology. It is very reasonably priced and I recommend it as one of the best basic neuroradiological texts available.

BRIAN KENDALL

Positron Emission Tomography in Dementia. *Frontiers in Clinical Neuroscience,* Volume 10. Edited by Ranjan Duara. 1990. New York: John Wiley.

PET has helped change the focus of attention in neurological diseases from distortions of structure to disorders of function. It provides measures of cerebral blood flow and metabolism which are direct reflections of regional brain activity, and can also be used to assess presynaptic neurotransmitter pools and quantify neurotransmitter receptors in vivo. Physiological variables, however, are difficult to interpret as indices of malfunction if they have high intrinsic variability in normal individuals. Cerebral metabolic rate for glucose has a coefficient of variation of about 20%, arising partly from methodological factors and partly from intrinsic variation. The most valuable contribution of this book is a thorough examination of the sources of variation in PET measurements.

In Chapter 1, Duara examines the intrinsic sources of variation in metabolism in normal individuals, and concludes that the most important variables are brain volume and brain atrophy. However, half of the variation in resting metabolic rate is not accounted for by known characteristics of the subjects. The fact that variation in cerebral metabolism within a single subject over a time scale of several weeks is comparable with intersubject variation suggests that much of the variance is due to transient changes in brain state.

Chapters 2, 3, 6 and 7 examine methodological issues in detail. Horwitz' account of the quantification of PET metabolic data in Chapter 2 is a clear presentation of the complex issues that arise at the levels of tomographic reconstruction, modelling of tracer kinetics, image analysis, and data interpretation, In Chapter 3, Chawluk *et al.* demonstrate the importance of correcting for atrophy. Their calculations suggest that the apparent parietal hypometabolism in Alzheimer's disease might be accounted for entirely by atrophy. Nevertheless, they acknowledge the technical limitations of their method of data analysis. Their findings emphasize the importance of developing satisfactory techniques for aligning structural and functional images.

Chapter 6 indicates the potential for utilization of behavioural activation paradigms in PET studies, though few such studies have been performed in demented patients. The authors present some of their own findings of the effects of neuropsychological activation during the half hour uptake phase of the fluorodeoxyglucose (FDG) method for measuring glucose metabolism, but the time scale of the FDG method is not suitable for well focused neuropsychological activation studies. In Chapter 7, Mash and Flynn review the techniques of radioligand PET studies. The potential for such studies to examine neurotransmitter systems in dementia has yet to be exploited.

Chapters 4 and 5 present the principal achievements of PET in exploring the nature of dementing illnesses. Haxby reviews the findings concerning dementia of Alzheimer type (DAT) and concludes that the major insights provided by PET studies are an awareness of the heterogeneity of brain malfunction in DAT, and that metabolic abnormalities precede neuropsychological impairments in early DAT. In Chapter 5, Mazziotta reviews PET studies of Huntington's disease. Studies of regional metabolism and of pre- and postsynaptic dopaminergic function yield results consistent with the known pathology of Huntington's disease. The reduced striatal metabolism found in established cases can also be detected in cases at risk of suffering from the condition. This chapter demonstrates best how the idea of monitoring pathology and its evolution in vivo is now achievable

Overall, this well-presented book is a comprehensive compilation of issues in PET technique relevant to studies of dementia, but it reflects the fact that the potential of PET to delineate the mechanisms of dementia has yet to be realized.

PETER LIDDLE

An Introduction to Neurotransmission in Health and Disease. Edited by P. Riederer, N. Kopp and J. Pearson. 1990. Pp. 398. Oxford: Oxford Medical Publications. Price £50.00.

To attempt to cover the neurochemistry of the normal nervous system and that occurring in a variety of disease states in a single volume would initially appear foolhardy. But the editors of this volume have taken on the task and to a large extent they have been highly successful. By being selective in the areas covered and by concentrating on present knowledge of nuerotransmission in the human and primate nervous system they have produced a comprehensive and informative work.

Judging from the reference lists the chapters of the book appear to have been written between 1984 and 1987. However, they are still remarkably up-to-date in most areas although inevitably time and events have overtaken some of the contents. The refreshing aspect of this volume is that the chapters were purpose written and were not the proceedings of some meeting. The emphasis placed on the basic organization and function of the nervous system is a factor which will make the book relevant over a prolonged period of time. The editors themselves must also be congratulated for the extent of their contribution to the contents. Pearson is an author or coauthor of 10 chapters and Kopp of 5.

The organization of the book is worthy of comment since this has been conceived in a manner which allows the nonexpert to understand the basis of a whole range of approaches to the study of the nervous system. There is an initial section comprising 7 chapters covering a range of general aspects of nervous system function. This includes the basis of neurotransmission, the use of toxins to study the nervous system, and the organization of catecholamine, peptide and amino acid systems in brain and spinal cord. Naturally it does not cover all transmitter substances (no mention of 5-HT, acetylcholine or many of the peptides). Naturally it does not cover all aspects of each subject (the section on toxins is particularly brief). But overall this collection of chapters produces a good basis on which to read and understand much of the rest of the volume. Subsequent sections cover specific areas where diseases of the nervous system might occur (neuroendocrinology; central and peripheral autonomic systems; locomotion; emotion, pain and addiction; higher cerebral function). In most cases these sections are prefaced with an introductory chapter to the subject area which leads to a greater insight into the content of the following more specialized contributions. Again, not all the potential areas are represented and the depth of coverage is variable. However, there is some mention of most of the major components that one might expect to find in a book of this kind.

In many ways it would be relatively easy to criticize this work. It could be argued that important topics are missing, that there is insufficient detail in many areas and that some current concepts of the function of the nervous system, the basis of disease states and the mechanism of drug action, are not included. However, the volume is intended as an introduction to the subject and this it achieves. I recommend the work to students of medicine and the neurosciences who will find it a useful and sound foundation on which to build their knowledge and interest in this continually expanding field.

PETER JENNER

Brain Organization and Memory: Cells, Systems and Circuits. Edited by James L. McGaugh, Norman M. Weinberger and Gary Lynch. 1990. Pp. 409. New York: Oxford University Press. Price £60.00.

This is the third in a series of volumes based on conferences held at the Center for the Neurobiology of Learning and Memory at Irvine, California. The three volumes have appeared at intervals of 2–3 yrs and one potential use of the book is as an update on recent developments in the field. Its value in this respect is diminished by the publication delay, however. The conference on which the present volume is based took place in 1987. Nonetheless, the series does give an interesting historical perspective. The main point one notices in looking at the three volumes is how little overlap there is between their contents. The most favourable interpretation of this diversity is that the rate at which exciting new discoveries are produced is such that the field is new born every couple of years. However, the same diversity is observed within each volume. In the present volume there are chapters on topics within the fields of human experimental psychology, animal learning theory, clinical neuropsychology, single cell recording, neuroanatomy, and mathematical models, to name but a few. One suspects that about half of all the neuroscientists and psychologists in the world could have contributed a chapter if asked. Of course, this is not a new phenomenon; learning and memory have always been the central concern of psychology and neuroscience, since all cognitive activity relies on them. Progress has undoubtedly been made in the disparate fields listed above, and some of the contributors give interesting accounts of their current views.

D. GAFFAN

How Monkeys See the World. By D. L. Cheney and R. M. Seyfarth. 1990. Pp. 377. Chicago: Chicago University Press. Price $28.75; £19.95.

The past decade has witnessed a remarkable phenomenon in terms of interdisciplinary interaction. The convergence of thinking in the area of animal minds has resulted in philosophers sitting in the African bush watching monkeys, behavioural ecologists using the experimental procedures of cognitive scientists in the field and cognitive scientists delving into the philosophy of mind. Among the behavioural ecologists, Dorothy Cheney and Robert Seyfarth played a seminal role in developing an entirely new dimension to field work. Beginning in the late 1970s, they used the well-established procedure of playing back taped vocalizations from hidden loudspeakers to ask questions about animals' knowledge about the world in which they lived. This book summarizes a decade of research on three groups of vervet monkeys living in Kenya's Amboseli National Park at the foot of Mount Kilimanjaro.

Being biologists, Cheney and Seyfarth bring a strong functional emphasis to their work. Their guiding question is always: how do the animals use their knowledge of the world in which they live to survive more effectively? For many species (but particularly monkeys and apes), survival means not just solving ecological problems, but also the often more important business of engineering one's way through a complex social world. Learning how to set up and use alliances against rivals, how to manipulate and deceive, who would make a powerful ally, who is related to whom—these are the everyday activities of the average primate. Cheney and Seyfarth argue that many of the conventional laboratory tests of animals' cognitive abilities may be misleading because they ignore the fact that animals' capacities have evolved to allow them to solve specific functional real-world tasks. They argue very strongly in the concluding chapters that intellectual capacities are modular, and that some species are likely to be more competent in some domains than others. Their experimental studies of vervets, for example, suggest that primates may be much more competent in the social sphere than in the ecological domain.

In order to try to explore monkeys' cognitive abilities in more detail, Cheney and Seyfarth carried out a series of experiments in which a particular vocalization by one individual was played back to a specific audience under very tightly defined conditions Thus, in order to determine whether the animals understood the nature of relationships, they played back the distress call of a particular infant to a set of three females (the mother and two other adult females) when the infant itself was out of sight. By recording each female's behaviour before and after the stimulus playback, they were able to show that, while the mother immediately looked in the direction of the loudspeaker hidden in the bush, the other two females always looked first at the mother, suggesting that they understood not only which infant was calling but also which female that infant belonged to. Other analyses demonstrated that monkeys were able to identify equivalences in relationships (of the kind A is related to B as C is related to me). Evidence of this kind points to sophisticated cognitive abilities that had hitherto been assumed to be limited to human beings.

One other key feature that has always been considered to be uniquely human is, of course, language. Using the same playback paradigm, Cheney and Seyfarth have been able to show that a number of the design features that are supposed to distinguish human language from animal communication will have to be abandoned. Vervet monkeys (and other species of mammals and birds) give alarm calls that are specific to particular types of predators. The experiments unequivocally demonstrate that the identity of the predator is conveyed solely in the auditory signal, that the correct referent for a particular call is learned (probably through social reinforcement) and that animals will habituate to a particular individual if it gives too many false alarms for a specific predator.

One of the central issues that preoccupies much of the book is the question of whether monkeys have a theory of mind. Do they understand what it is to see the world from someone else's point of view? Behavioural biologists have made extensive use of the hierarchy of intensionality introduced from the philosophy of mind by Dan Dennett. Much of the emphasis has concentrated on the question of whether animals engage in deception, since deception is only possible if the animal can aspire to at least third order intensionality ('I want you to think that I intend to do X—when I am really intending to do Y'). To date, the bulk of the evidence has been anecdotal and somewhat equivocal, the only exception being Premack's experimental studies of the language-trained chimpanzee Sarah.

From a detailed analysis of both their own field experiments on vervet monkeys and other laboratory and field research on monkeys and apes, Cheney and Seyfarth conclude that while monkeys are good ethologists, they make poor psychologists. They are expert at reading other animals' behaviour, but not at reading their minds. They find it difficult to see the world wholly from another individual's point of view. Thus one of their males managed to keep a prospective immigrant away from his group for several days by giving intermittent alarm calls every time the rival approached the group too closely. But he eventually gave the game away by giving alarm calls while walking nonchalantly across open ground towards the trees in which the rival was sitting. His behaviour was like that of a human 3-year-old that vehemently denies having been at the biscuit tin while its face is covered in biscuit crumbs.

But if monkeys lack this key feature, it seems likely that apes have it. Indeed, there appears to be a major cognitive rift between the monkeys and the apes. Chimpanzees, at least, exhibit many of the other features that seem to characterize human beings, such as engaging in pretend play and tool-making. But even apes lack one key behavioural feature that seems otherwise unique to humans, namely the ability to console another individual. Apes can grieve for the loss of a companion, but other apes do not comfort them: that requires the ability to empathize, to see the world from someone else's point of view, to have, as Premack has put it, a theory of mind. But while this is true, I wonder how much behaviour of this kind is dependent on language alone. Would humans engage in such behaviour if they had not been taught to see the world from someone else's point of view? Do we have an *innate* theory of mind, or is it only an emergent property of the pedagogical opportunities provided by language?

This is an important book that raises issues of significance to a number of disciplines operating in the cognitive sciences. Cheney and Seyfarth not only review their own work, but place it in the context of both the work on other species and the discussions of these issues by philosophers, linguists, psychologists and neurobiologists. Their approach is cautious and balanced: they are careful to stress both the difficulty of making clear-cut inferences from studies of this kind and the unavoidably speculative nature of some of their conclusions. But for all that, what they have to say is challenging and exciting. It will, I hope, persuade both neurobiologists and psychologists that it is possible to do well-controlled experiments on wild animals and that they have something to learn from what ethologists can tell them about the naturalistic behaviour of animals.

R. I. M. DUNBAR

ANNOUNCEMENTS

International Quincke Symposium

This symposium, organized under the auspices of the World Federation of Neurology, will be devoted to Barrier Concepts and Cerebrospinal Fluid Analysis. It will be held in Göttingen, on September 19–21, 1991. For information, contact Professor K. Felgenhauer, Neurologische Universitatsklinik, Robert-Koch-Strasse 40, D-3400 Gottingen, Germany.

European Neurological Society

The third meeting will be held at the Palais de Beaulieu, Lausanne, Switzerland, on June 27–July 1, 1992 The deadline for the receipt of abstracts is January 15, 1992. Further information may be obtained from Professor Andreas Steck, Service de Neurologie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.

American Association of Electrodiagnostic Medicine

The annual scientific meeting of the AAEE will be held in Vancouver, British Colombia, Canada, on September 25–28, 1991 The theme of the plenary session will be diabetic neuropathies. For further information, contact the AAEM, 21 Second Street SW, Suite 36, Rochester MN 55902, USA (Fax. 507/288–1225; Tel: 507/288–0100).

NEW FROM OXFORD

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Cerebral Localization and Its Biological Context from Gall to Ferrier
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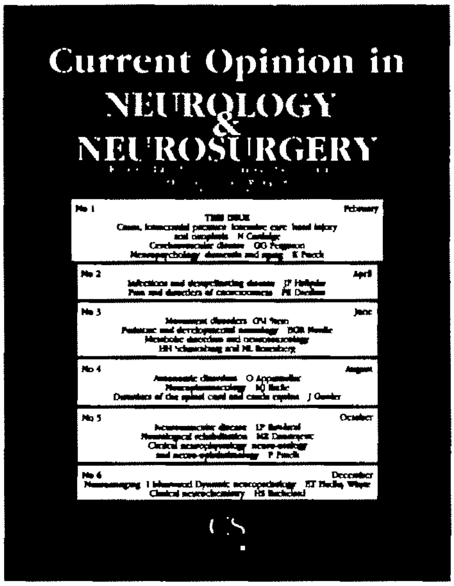

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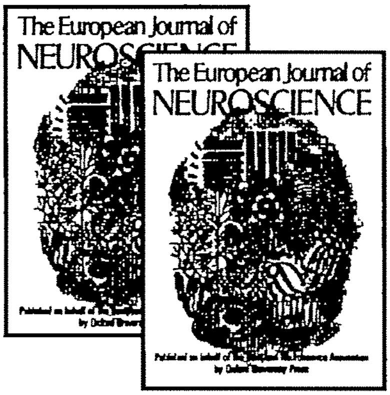
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Editorial Policy

Brain has long been the natural place to publish definitive studies in neurology and related clinical disciplines and in the neurosciences when they lead to an improved understanding of disease mechanism. The new editorial team aims to continue this broad policy.

Neurology has expanded rapidly in the past decade and at the present time advances in our understanding of aetiology, pathogenesis and treatment depend on techniques derived from fields as different as anatomy, biochemistry, cell biology, clinical medicine, electrophysiology, immunology, mathematics, molecular genetics, physics, psychology, and virology. Such diversity means that few can encompass the technical aspects of more than one or two of the relevant disciplines. The journal aims to maintain a balance in the papers from different fields and it therefore looks for contributions in which there is not only sufficient technical detail given to enable the work to be repeated, but in which the presentation makes clear to the non-expert the principles of the investigative approach.

Such a policy does not necessarily imply that great length is required. Indeed, we welcome short papers when a clear answer to an important question can be persuasively presented in a few pages. Nevertheless, it is important that there should be a forum for the publication of extended original articles and reviews and this *Brain* will continue to provide. The essential criterion is that the size of the paper should be matched to the importance of the message it contains. Given that we aim to provide a balanced coverage of the field, it is inevitable that from time to time restrictions will have to be placed on the numbers of articles accepted on particular topics. Such decisions are difficult, and the Editorial Board will review them at its regular meetings.

A pressing consideration is that of speed of publication. We are determined that it should be reduced, the limiting factor being the maintenance of the highest standards of peer review and production. A most important step forward has been the appointment of the first full time Assistant Editor for *Brain*, Dr Carol Lovelidge, who has experience in research in neuroscience. With the enthusiastic help of Oxford University Press, a number of ways in which the publication process can be speeded up has been identified. We aim too to increase the efficiency of the refereeing process. Again, OUP has been helpful in making available a computerized system for keeping track of papers and referees' responses. With these changes we expect by the commencement of the next volume to have papers published within six months of acceptance.

W.I. McDonald

Brain (1991), 114, 2025–2036

REFLEX SYMPATHETIC DYSTROPHY: THE SIGNIFICANCE OF DIFFERING PLASMA CATECHOLAMINE CONCENTRATIONS IN AFFECTED AND UNAFFECTED LIMBS

by PETER D. DRUMMOND,[1] PHILIP M. FINCH[2] *and*
GEORGE A. SMYTHE[3]

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SUMMARY

In 26 patients with features of reflex sympathetic dystrophy, venous blood was collected from painful and unaffected limbs. Levels of plasma adrenaline, noradrenaline and its intracellular metabolite, 3,4-dihydroxyphenylethyleneglycol (DHPG), were measured by combined' gas chromatography/mass spectrometry.

Plasma DHPG was lower on the painful side. Concentration of plasma noradrenaline was also lower on the painful side in patients with widespread allodynia, and in those with hyperhidrosis in the affected hand or foot. These findings do not support the widely held view that autonomic disturbances in reflex sympathetic dystrophy are due to sympathetic overactivity. Rather, they suggest that sweating and changes in peripheral blood flow result from supersensitivity to sympathetic neurotransmitters.

After injury, supersensitivity to noradrenaline may also contribute to spontaneous pain and allodynia by disrupting efferent sympathetic modulation of sensation. This would explain why pain and allodynia are relieved by sympathetic blockade, and why noradrenaline rekindles pain in sympathectomized skin.

INTRODUCTION

It has been assumed that an increase in sympathetic outflow causes sweating and changes in peripheral blood flow in reflex sympathetic dystrophy (RSD) (Bonica, 1979). In fact, the basis of current treatment for this condition centres around reducing sympathetic outflow to the affected limb. However, confirming that sympathetic outflow is increased has proved to be suprisingly difficult. For example, multi-unit micro-electrode recordings of sympathetic outflow to affected skin were found to be qualitatively normal in their response to arousal stimuli (Wallin *et al.*, 1976; Torebjörk and Hallin, 1979; H. Blumberg and R. Dotson, personal communications). Furthermore, vasoconstrictor tone was found to be reduced rather than increased in symptomatic areas (Christensen and Henricksen, 1983; Rosén *et al.*, 1988).

The most direct way to study sympathetic outflow quantitatively would be to record neural activity simultaneously from painful and normal skin. Unfortunately, micro-electrode recordings are difficult to calibrate because the signal is altered by slight adjustments to the position of the electrode tip. In addition, positioning the electrode

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correctly is technically difficult, and the procedure can be painful. Possibly for these reasons, such studies have not been reported.

We investigated sympathetic outflow indirectly in patients with features of RSD by measuring concentrations of plasma noradrenaline and its intracellular metabolite, 3,4-dihydroxyphenylethyleneglycol (DHPG). Venous blood was taken from the painful and normal limbs. Concentration of plasma adrenaline was also measured in some patients. Since adrenaline is released from the adrenal medulla, levels should be similar on both sides of the body if both limbs are kept in similar environments. Differing plasma concentrations in the painful and normal limbs would then indicate that the local clearance rate differed on the two sides. Skin temperature of the fingers and toes was used as an indirect index of blood flow.

The purpose of our study was to determine whether catecholamine concentrations were increased or decreased on the painful side in patients with RSD. Lower concentrations of noradrenaline in the painful limb would suggest that supersensitivity of target organs contributes to autonomic disturbances in RSD (Jänig, 1990).

METHOD

Subjects

Twenty-six patients considered clinically to have features of RSD were studied (Table 1). Each patient received a neurological and general physical examination and was investigated by appropriate laboratory procedures (e.g. technetium bone scan, neuroradiological imaging, electrophysiological studies, arthroscopy) to identify organic pathology. In all except 2 cases, pain first started after injury to a limb. In one patient pain was associated with cervical radiculopathy, and in the other patient pain started after an almost complete brachial plexus injury.

TABLE 1. CLINICAL CHARACTERISTICS

	Age	*Sex*	*Initial injury*	*Duration (mths)*	*General allodynia*	*Sweating*	*Temperature difference (°C)*	*Response to sympathetic blockade*	*Relief > 24 h*
1.	45	F	Injury to elbow with entrapment radial sensory n. and lateral cutaneous n. forearm	26	++	+	−0.6	complete	+
2.	20	F	Post-traumatic neuroma superficial peroneal n	4	++	+	1 0	complete	+
3	20	F	Blow to radial side of wrist	23	++	before sympathectomy	−5.8	complete	+
4.	53	F	Median n. laceration and repair	5	++	−	−0.1	complete	+
5.	48	F	Smith's fracture wrist	3	+	+	3.7	complete	+
6.	32	F	Blow to patella	66	+	+	0.6	complete	+
7.	45	F	Post-traumatic neuroma deep peroneal n	3	+	−	−0.2	complete	+
8.	50	F	Stump neuroma of amputated finger	7	−	−	−1.3	complete	+
9.	32	M	Injury to wrist with entrapment and release of median n.	5	−	+	−0.2	complete	−

	Age	*Sex*	*Initial injury*	*Duration (mths)*	*General allodynia*	*Sweating*	*Temperature difference (°C)*	*Response to sympathetic blockade*	*Relief > 24 h*
10.	41	F	Almost complete brachial plexus avulsion injury, minor recovery C5	116	–	–	−0.2	complete	+
11.	20	F	Soft tissue crush injury knee, L5S1 spinal stenosis, disc protrusion	19	++	–	0.0	partial	–
12	38	F	Cervical radiculopathy C6–7	36	++	+	−0.7	partial	–
13.	36	M	Median n. release for neuropathy	30	++	+	−1.0	partial	–
14.	71	F	Total hip replacement, possible neuropraxia S1	2	+	–	1.6	partial	+
15.	47	M	Injury to knee and ankle with tarsal tunnel entrapment	15	+	–	−1.0	partial	–
16	39	F	Occupational over-use syndrome upper limb	2	+	–	0.7	partial	–
17.	39	F	Injury to elbow with entrapment of radial sensory n. and possibly lateral cutaneous n. forearm	38	+	–	1.0	partial	+
18.	41	M	Crush injury to dorsum of hand, possible radial n damage	24	+	+	−0.1	partial	–
19.	31	M	Post-traumatic arthropathy of knee	84	–	–	1.7	partial	–
20	25	M	Ulnar n. injury and transposition	17	–	+	0.0	partial	–
21.	44	F	Post-traumatic radial digital n. neuroma	6	–	–	−0.5	partial	–
22.	34	F	Injury to elbow and wrist with entrapment radial sensory n.; released then re-injured	38	–	–	−0.3	partial	–
23.	17	F	Median n injury, released twice	10	+	+	0.3	no change	–
24.	16	M	Forced dorsiflexion wrist, possible ulnar n. injury	2	+	–	−0.4	no change	–
25.	36	M	Post-traumatic arthropathy of shoulder	5	–	+	−0.1	no change	–
26.	37	M	Fracture of oscalcis	46	–	+	2.3	no change	–

Patients are ranked by their response to sympathetic blockade, and then by the severity of allodynia. A positive temperature difference indicates that the affected side was warmer then the other side.

In 17 patients a light stimulus anywhere in the symptomatic limb provoked a painful sensation (allodynia). Whether allodynia was mild or severe was gauged by the patient's behavioural and verbal response to gently touching or tapping the skin (Table 1).

In 12 patients the palm of the hand or sole of the foot was moist to touch on the painful side during the physical examination, whereas the opposite extremity was dry (Table 1). In one other patient excessive sweating had been abolished by a transthoracic sympathectomy.

Blood samples were also collected from 3 male and 3 female normal controls aged between 27 and 53 yrs (mean age 38 yrs).

All subjects gave their informed consent for the procedures, which were approved by the Murdoch University Ethics Committee.

Procedure for patients

Blood samples were collected from patients while they lay on a hospital bed in a recovery room maintained at 22 ± 1 °C. About 30 min after entering the recovery room, catheters or butterfly needles were inserted into a vein draining the symptomatic area (usually the dorsal venous arch of the hand or foot), and into a similar vein on the opposite limb; needles were kept patent with heparinized saline.

Twenty minutes later, skin temperature of the middle phalanx on the dorsal aspect of each finger or toe was measured to the nearest 0.1 °C with a C600-M Biotherm infra-red thermometer (Linear Laboratories, Mountain View, CA). A recording was taken on the painful side, then on the other side, until all 10 values were obtained. Mean finger or toe temperature was later calculated for the painful and normal sides.

After an initial 2 ml had been withdrawn and discarded, 20 ml of blood was collected from each catheter. The blood was placed in a cooled tube containing EGTA (0.25 mol/l) and glutathione (0.20 mol/l) and kept on ice until spun. Samples were taken from the painful side first in 16 of the 26 patients.

As part of the diagnostic procedure, the stellate ganglion or lumbar sympathetic chain was then blocked on the affected side with 10 ml of 0.5% bupivacaine. In each case, signs of sympathetic blockade (warm, flushed skin, loss of sweating, or Horner's syndrome) were observed on the appropriate side shortly after the injection. Spontaneous pain and allodynia were assessed clinically 1 h after sympathetic blockade.

Control subjects

Skin temperature of the fingers was measured, and venous blood samples were collected from the upper limbs of 3 male and 3 female normal controls using the procedures described above. After blood samples were obtained, one hand was immersed in a water-bath at 15 °C for 2 min. Ten minutes later, further samples were collected from both limbs and finger temperature was measured.

Biochemistry

Samples were spun for 10 min at 2400 r.p.m. in centrifuge buckets cooled initially to −40 °C. The plasma was separated and stored at −40 °C until assayed.

Adrenaline, noradrenaline, and its primary neuronal metabolite, DHPG, were assayed blind by gas chromatography/mass spectrometry (Hewlett-Packard 5987A data system, North Ryde, NSW), using the negative-ion chemical ionization technique (Faull and Barchas, 1983). All analytical data were obtained using the selected ion-monitoring mode. The coefficient of variation between assays for these compounds has been established to be 2.5–4.0%, and sensitivity to be less than 200 fmol for each compound. Precisely known amounts of deuterated internal standards (d3-noradrenaline, d2-DHPG, and d3-adrenaline, MSD Isotopes, Quebec, Canada) were added to each 2 ml plasma sample. The extraction and derivatization procedures have been described in detail elsewhere (Duncan *et al.*, 1985). The results are expressed as nanomole per litre of plasma (nmol/l).

Data analyses

Paired data were compared with Wilcoxon's matched-pairs signed-ranks test, and relationships among variables were investigated with Spearman's rho. Non-parametric statistics were computed because the distribution of values around the mean differed substantially from normal for adrenaline, noradrenaline and DHPG. Differences between the painful and normal sides were investigated in subgroups of patients defined by the presence or absence of widespread allodynia, the presence or absence of sweating on the painful side during the clinical examination, and by the response to sympathetic blockade.

Patient 3 (Table 1) had features of reflex sympathetic dystrophy which had recurred 19 mths after transthoracic sympathectomy. Because the sympathectomy may have influenced catecholamine levels in the affected limb, her data were not included in statistical analyses and are reported separately.

RESULTS

Control subjects

Levels of plasma adrenaline and noradrenaline were greater on the side sampled first (Table 2). In contrast, the order of collection did not influence DHPG levels. Apart from skin temperature, no difference between sides was detected after cooling one hand (Table 3).

TABLE 2 CATECHOLAMINE CONCENTRATIONS AND SKIN TEMPERATURE IN 6 CONTROL SUBJECTS

	Mean ± SD		*Wilcoxon's*	
	First side	*Second side*	*z*	*P*
DHPG (nmol/1)	6.9 ± 1 5	6 6 ± 1.3	1.15	–
Noradrenaline (nmol/l)	2.4 ± 0.4	1.9 ± 0.3	2.20	< 0.05
Adrenaline (nmol/l)	0.59 ± 0 28	0 35 ± 0.16	1.99	< 0.05
Temperature (°C)	32.3 ± 2.5	32.2 ± 2 5	0.37	–

TABLE 3 CATECHOLAMINE CONCENTRATIONS AND SKIN TEMPERATURES IN 5* CONTROL SUBJECTS, 10 MIN AFTER COOLING ONE HAND

	Mean ± SD		*Wilcoxon's*	
	Cooled side	*Other side*	*z*	*P*
DHPG (nmol/l)	7.5 ± 1.6	7.5 ± 1.8	0.40	–
Noradrenaline (nmol/l)	2.0 ± 0.6	1.9 ± 0 3	0 67	–
Adrenaline (nmol/l)	0.39 ± 0.22	0.38 ± 0.16	0.40	–
Temperature (°C)	33.0 ± 0.9	28.3 ± 4.8	2.02	< 0.05

* Data was lost in one subject due to technical problems

Clinical characteristics of patients

Seven patients had extreme allodynia extending well beyond the original site of injury (graded '+ +' in Table 1). Allodynia was widespread but mild in another 10 cases (graded '+'). Increased sweating was detected on the painful extremity in 12 patients during the clinical examination. Skin temperature did not differ consistently between the 2 sides (Table 4), but was greater by at least 1 °C on the painful side in 6 patients, and on the normal side in 4 patients.

Catecholamine concentrations in patients

The level of DHPG was lower on the painful side than on the normal side (Table 4). Plasma noradrenaline levels were lower on the painful side in patients with widespread allodynia, and in those with a sweaty hand or foot during the clinical examination (Table 5). No difference between sides was detected for concentration of plasma

TABLE 4 CATECHOLAMINE CONCENTRATIONS AND SKIN TEMPERATURE ON THE SYMPTOMATIC AND NON-SYMPTOMATIC SIDES

		Mean ± SD		*Wilcoxon's*	
	N	*Painful*	*Normal*	*z*	*P*
DHPG (nmol/l)	16	8.5±3.7	9.9±3.8	2.27	< 0.05
Noradrenaline (nmol/l)	25	3.4±2.0	3.8±2.4	1.53	–
Adrenaline (nmol/l)	16	0.38±0.24	0.38±0.39	0.93	–
Temperature (°C)	25	31.8±3.8	31.5±4.0	0.81	–

TABLE 5 CONCENTRATION OF PLASMA NORADRENALINE ON THE PAINFUL AND NORMAL SIDES IN RELATION TO GENERALIZED ALLODYNIA, AND SWEATING

		Mean ± SD (nmol/l)		*Wilcoxon's*	
	N	*Painful*	*Normal*	*z*	*P*
Allodynia					
Present	16	3.4±1.7	4.3±2.8	2.02	< 0.05
Absent	9	3.5±2.7	3.0±1.5	0.12	–
Sweating					
Present	12	3.8±2.1	4.8±3.0	2.09	< 0.05
Absent	13	3.1±2.1	2.9±1.3	0.14	–

adrenaline (Table 4). Plasma DHPG was measured in 2 of 4 patients who did not respond to sympathetic blockade (patients 25 and 26, Table 1). Levels were lower by 1.2 nmol/l on the painful side in both cases.

The temperature difference between the 2 sides was related to differences in adrenaline [Spearman's rho (24 df) $= 0.49$, $P = 0.05$] but not to differences in noradrenaline or DHPG. Thus, concentration of plasma adrenaline was usually lower on the painful side if it was cooler than the normal side.

No consistent relationship was detected between duration of the condition, and differences between the painful and normal limbs in skin temperature or catecholamine concentrations.

Response to sympathetic blockade

In 10 patients spontaneous pain and allodynia disappeared after sympathetic blockade ('complete' response in Table 1). In another 12 cases spontaneous pain and allodynia decreased but were still present ('partial' response in Table 1). No change in pain was reported by the other 4 patients. Relief lasted for more than 24 h in 11 cases.

Concentration of plasma noradrenaline was 0.8 to 3.9 nmol/l lower on the painful side in 6 of 7 patients whose allodynia and spontaneous pain were relieved completely by sympathetic blockade (patients 1–6, Table 1). A similar result was obtained in only one other patient whose pain responded partially to sympathetic blockade (patient 12, Table 1). Levels were marginally (0.1–0.7 nmol/l) lower on the painful side in 7 patients, and on the normal side in another 8 patients. In only 3 cases (patients 8, 17 and 26, Table 1), concentration of plasma noradrenaline was greater on the painful side by more than 0.8 nmol/l. These 3 patients had different clinical features, and responded differently to sympathetic blockade (Table 1).

Case report

Patient 3 (Table 1) injured her left wrist while playing volleyball. She developed paraesthesiae in her left hand, which became cool and sweaty compared with the right. After a series of stellate ganglion blocks and guanethidine infusions, she had a transthoracic sympathectomy. Her left hand was warm and painless for 19 mths, but several weeks before the investigation paraesthesiae over the left scapula, piloerection in the left hand and coldness, pain and allodynia in the entire left arm gradually returned. Thus, the development of pain appeared to coincide with partial sympathetic reinnervation.

On examination, her left hand was almost 6°C cooler than the right, but did not sweat. Levels of plasma noradrenaline, DHPG and adrenaline were *lower* on the affected side by 2.9 nmol/l, 8.9 nmol/l and 2.4 nmol/l, respectively. Hence, vasoconstriction and piloerection were more likely to be due to denervation supersensitivity than to excessive sympathetic outflow. After stellate ganglion blockade, the left limb became warm and pain-free. Long-term relief was obtained after a radiofrequency lesion of the stellate ganglion.

DISCUSSION

Reflex sympathetic dystrophy usually starts after minor injury to a limb, particularly in a region rich in nerve endings (Bonica, 1979). Autonomic disturbances are often prominent in RSD, and pain on light touch (allodynia) may spread to include the whole limb. In the early stages of the condition, pain usually responds to sympathetic blockade or sympathetic denervation (Bonica, 1979; Ghostine *et al.*, 1984). All of our patients had chronic pain which persisted long after the initial injury had time to resolve, and pain responded at least partially to sympathetic blockade in all but 4 cases. Most patients also had other features of RSD, such as widespread allodynia, hyperhidrosis, or changes in blood flow in the affected limb. Thus, they appeared to be representative of patients considered clinically to have RSD.

Methodological issues

Our plasma samples were assayed by combined gas chromatography/mass spectrometry, with deuterated internal standards for analysis of all samples. This approach is more specific than other analytical methods (Duncan *et al.*, 1985). The precision of the technique could be important when investigating regional differences within subjects.

Eckberg *et al.* (1988) reported that the level of plasma noradrenaline in blood drawn from the antecubital vein corresponded closely to peroneal nerve muscle sympathetic activity recorded directly with micro-electrodes. Providing that levels are not influenced greatly by the local clearance rate, concentration of noradrenaline in venous blood from the hand or foot should vary in proportion to local sympathetic outflow. We compared the clearance rate of catecholamines from painful and normal limbs by measuring plasma concentration of adrenaline. This level did not differ significantly between painful and normal limbs, but was lower on the cooler side. In contrast, levels of noradrenaline and DHPG did not differ between the cooler and warmer sides, suggesting that rate of blood flow did not influence their clearance rates to any great extent. Furthermore, concentrations of noradrenaline and DHPG were similar in cooled and uncooled hands of control subjects.

We attempted to minimize stress reactions during blood collection by inserting catheters at least 20 min before blood was withdrawn. Despite this precaution, levels of adrenaline and noradrenaline were higher on the side sampled first in control subjects. Blood was taken from the painful side first in 16 of 26 patients; if anything, this should have worked against the direction of the obtained results. The level of DHPG was not influenced by order of sampling in control subjects. Thus, it is significant that the level was lower on the painful side in our patients. DHPG is produced by intraneuronal metabolism of noradrenaline after re-uptake (Fig. 1). Since it is produced locally, DHPG may reflect local sympathetic activity more accurately than noradrenaline.

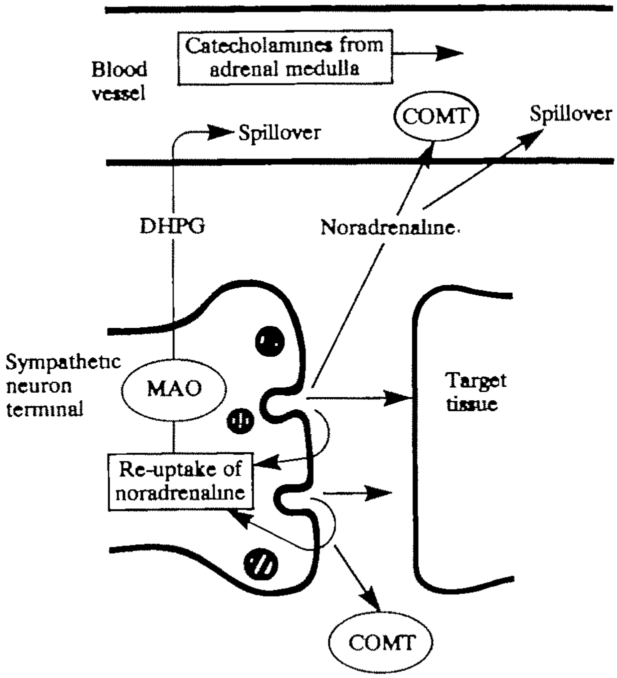
Blood vessel
Catecholamines from adrenal medulla
Spillover
COMT
Spillover
DHPG
Noradrenaline
Sympathetic neuron terminal
MAO
Target tissue
Re-uptake of noradrenaline
COMT

FIG. 1. Source of noradrenaline and DHPG in venous blood (not drawn to scale). After being released into the synaptic cleft, noradrenaline diffuses across the synapse to bind to receptors on the target tissue, and is rapidly metabolized by catechol-O-methyltransferase (COMT). Some noradrenaline escapes degradation and diffuses through the extracellular fluid to capillaries where it mixes with catecholamines released from the adrenal medulla. Noradrenaline taken up by the presynaptic neuron is held for re-use or metabolized by monoamine oxidase (MAO) to DHPG.

Nature of the autonomic disturbance in RSD

The level of plasma noradrenaline was lower on the painful side in patients with clearly increased sweating of the hand or foot. Sweating is mediated primarily by acetylcholine but other neurotransmitters, including noradrenaline, may also be involved (Shields *et al.*, 1987). Locally released noradrenaline does not by itself stimulate sweating, but could do so in combination with circulating catecholamines. Sweat glands may develop denervation supersensitivity. For example, Low *et al.* (1983) reported that sweating in response to electrophoresis of acetylcholine was sometimes exaggerated in partially denervated areas in patients with postganglionic sympathetic lesions. Hence, our findings in patients with RSD are more consistent with adaptive supersensitivity than with sympathetic overactivity. Whether partially denervated sweat glands develop supersensitivity to catecholamines has not been investigated.

As in previous studies (Shumacker *et al.*, 1948; Tahmoush *et al.*, 1983), the painful hand or foot was cooler than the opposite extremity in some of our patients, and warmer in others. Shortly after injury, the affected region in RSD is said to be warm, dry and red but later on the skin becomes cool and sweaty (Bonica, 1979). We did not find a relationship between asymmetry of skin temperature and duration of pain, but clear differences between sides were detected in some patients. Sympathetic vasomotor outflow may be reduced in patients with RSD. In 6 patients studied by Christensen and Henricksen (1983), proximal nervous blockade caused an increase in subcutaneous blood flow of only 35% in the affected hand compared with an increase of 122% on the other side. Thus, vasoconstrictor tone apparently was lower on the painful side. Rosén *et al.* (1988) reported recently that nailfold-skin capillary blood cell velocity, and skin blood flow through the affected finger assessed by laser Doppler flowmetry, were lower in 12 patients with RSD than in controls. In addition, reflexes to skin cooling and postural changes were impaired in the affected finger, indicating reduced sympathetic function.

Campbell *et al.* (1988) suggested that patients with chronic pain and hyperalgesia should be grouped into those with sympathetically maintained pain, and those whose pain is not affected by sympathetic activity, by their response to sympathetic blockade. We are not able to compare these groups statistically, because all but 4 of our patients reported at least partial improvement after sympathetic blockade. Nevertheless, it is worth noting that the reduction in plasma noradrenaline on the painful side was observed most consistently in patients whose spontaneous pain and allodynia were relieved completely by sympathetic blockade. Thus, sympathetically maintained pain appears to be associated with reduced sympathetic outflow in the painful limb.

Interaction between sympathetic and sensory nerves in RSD

Wallin *et al.* (1976) found that allodynia could be rekindled in sympathectomized skin after iontophoretic application of noradrenaline. Hence, pain in RSD appears to depend critically on the level of noradrenaline in pain-sensitized skin.

Jänig (1990) hypothesized that a vicious circle of excitation of primary afferent fibres by postganglionic sympathetic axons maintains the pathophysiological process in RSD. The circle is interrupted by sympathetic blockade. Experimentally produced neuromas in rats develop alpha-adrenergic chemosensitivity (Devor, 1983). A similar process could increase pain at the site of injury in RSD, and may also contribute to allodynia in surrounding skin (Devor, 1983). Other types of coupling between sensory and sympathetic fibres in RSD are also possible. In a pharmacological model of hyperalgesia described by Levine *et al.* (1986), noradrenaline stimulated release of prostaglandins from postganglionic sympathetic fibres sensitized by chloroform. The prostaglandins then provoked pain.

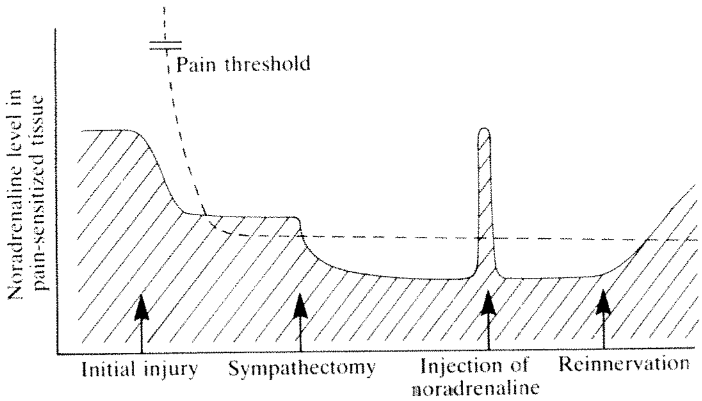
Pain threshold
Noradrenaline level in pain-sensitized tissue
Initial injury
Sympathectomy
Injection of noradrenaline
Reinnervation

FIG. 2. Hypothesized interaction between pain and sympathetic outflow in RSD. Sympathetic outflow decreases after the initial injury, possibly because of direct damage to sympathetic fibres, or indirectly due to other peripheral or cental changes. The fall in sympathetic outflow stimulates adaptive supersensitivity in blood vessels and sweat glands. Disruption of the normal modulation of sensation by sympathetic outflow, or development of neuromas or microneuromas, could mediate sympathetically maintained pain. Alternatively, pain could be caused by prostaglandins, released by noradrenaline from sensitized postganglionic sympathetic nerve terminals. Sympathectomy prevents, but does not cure, pain sensitization by noradrenaline. Thus, increases in noradrenaline by injection or iontophoresis, or after reinnervation of sympathetic fibres (as in the case report), will provoke pain.

Central to most theories of the mechanism of RSD is a disruption of information processing in the spinal cord or brain (Jänig, 1990). Roberts (1986) suggested that wide dynamic range neurons in the spinal cord become sensitized by intense noxious stimulation in RSD. Activity in low-threshold, myelinated mechanoreceptors, stimulated directly or indirectly by sympathetic outflow, then excites sensitized spinal neurons and causes pain.

Hypothesis

The view that increased sensitivity of spinal reflexes increases sympathetic activity in the affected limb in RSD (Bonica, 1979) was not confirmed by our data. In fact sympathetic outflow, indexed by concentration of plasma noradrenaline and its intraneuronal metabolite, DHPG, was *lower* on the painful side in patients with the fully developed condition.

Could a *fall* in sympathetic outflow contribute to spontaneous pain and allodynia in RSD? After tissue injury, a local decrease in release of sympathetic neurotransmitters could induce adaptive supersensitivity in blood vessels and sweat glands. By analogy, afferent neurons or their sensory receptors could also develop supersensitivity to adrenergic substances (Sato and Perl, 1991) (Fig. 2). We suggest that adrenergic supersensitivity aggravates the primary pain-producing mechanism in RSD, either in the periphery (Devor, 1983; Levine *et al.*, 1986) or in the spinal cord (Roberts, 1986; Schott, 1986). Further study of the mechanism of this disabling condition is needed for more effective treatment.

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REFERENCES

BONICA JJ (1979) Causalgia and other reflex sympathetic dystrophies *Advances in Pain Research and Therapy*, **3**, 141–166.

CAMPBELL JN, RAJA SN, MEYER RA (1988) Painful sequelae of nerve injury. In. *Proceedings of the Vth World Congress on Pain.* Edited by R. Dubner, G. F. Gebhart and M. R. Bond Amsterdam: Elsevier, pp. 135–143.

CHRISTENSEN K, HENRIKSEN O (1983) The reflex sympathetic dystrophy syndrome: an experimental study of sympathetic reflex control of subcutaneous blood flow in the hand. *Scandinavian Journal of Rheumatology*, **12**, 263–267.

DEVOR M (1983) Nerve pathophysiology and mechanisms of pain in causalgia *Journal of the Autonomic Nervous System*, **7**, 371–384.

DUNCAN MW, SMYTHE GA, CLEZY PS (1985) Gas chromatographic/mass spectrometric methodology for simultaneous assay of salsolinol, dopamine, norepinephrine, dihydroxyphenylacetic acid and dihydroxyphenylethanol. *Biomedical Mass Spectrometry*, **12**, 106–114.

ECKBERG DL, REA RF, ANDERSSON OK, HEDNER T, PERNOW J, LUNDBERG JM *et al.* (1988) Baroreflex modulation of sympathetic activity and sympathetic neurotransmitters in humans. *Acta Physiologica Scandinavica*, **133**, 221–231.

FAULL KF, BARCHAS JD (1983) Negative-ion mass spectrometry fused-silica capillary gas chromatography of neurotransmitters and related compounds. *Methods of Biochemical Analysis*, **29**, 325–383.

GHOSTINE SY, COMAIR YG, TURNER DM, KASSELL NF, AZAR CG (1984) Phenoxybenzamine in the treatment of causalgia: report of 40 cases. *Journal of Neurosurgery*, **60**, 1263–1268.

JANIG W (1990) The sympathetic nervous system in pain: physiology and pathophysiology. In: *Pain and the Sympathetic Nervous System.* Edited by M. Stanton-Hicks. Boston and London: Kluwer Academic, pp. 17–89.

LEVINE JD, TAIWO YO, COLLINS SD, TAM JK (1986) Noradrenaline hyperalgesia is mediated through interaction with sympathetic postganglionic neurone terminals rather than activation of primary afferent nociceptors. *Nature, London*, **323**, 158–160.

LOW PA, CASKEY PE, TUCK RR, FEALEY RD, DYCK PJ (1983) Quantitative sudomotor axon reflex test in normal and neuropathic subjects. *Annals of Neurology*, **14**, 573–580.

ROBERTS WJ (1986) A hypothesis on the physiological basis for causalgia and related pains. *Pain*, **24**, 297–311.

ROSÉN L, ÖSTERGREN J, FAGRELL B, STRANDEN E (1988) Skin microvascular circulation in the sympathetic dystrophies evaluated by videophotometric capillaroscopy and laser Doppler fluxmetry. *European Journal of Clinical Investigation*, **18**, 305–308.

SATO J, PERL ER (1991) Adrenergic excitation of cutaneous pain receptors induced by peripheral nerve injury. *Science*, **251**, 1608–1610.

SCHOTT GD (1986) Mechanisms of causalgia and related clinical conditions: the role of the central and of the sympathetic nervous systems. *Brain*, **109**, 717–738.

SHIELDS SA, MACDOWELL KA, FAIRCHILD SB, CAMPBELL ML (1987) Is mediation of sweating cholinergic, adrenergic, or both? A comment on the literature. *Psychophysiology*, **24**, 312–319.

SHUMACKER HB, SPEIGEL IJ, UPJOHN RH (1948) Causalgia: II. The signs and symptoms, with particular reference to vasomotor disturbances. *Surgery, Gynecology and Obstetrics*, **86**, 452–460.

TAHMOUSH AJ, MALLEY J, JENNINGS JR (1983) Skin conductance, temperature, and blood flow in causalgia. *Neurology, Cleveland*, **33**, 1483–1486.

Torebjörk HE, Hallin RG (1979) Microneurographic studies of peripheral pain mechanisms in man. *Advances in Pain Research and Therapy*, **3**, 121 – 131.

Wallin G, Torebjörk E, Hallin R (1976) Preliminary observations on the pathophysiology of hyperalgesia in the causalgic pain syndrome. In: *Sensory Functions of the Skin in Primates: with Special Reference to Man. Wenner-Gren Center International Symposium Series*, Volume 27. Edited by Y. Zotterman. Oxford: Pergamon Press, pp. 489 – 502.

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MATURATION OF HUMAN CEREBRUM OBSERVED *IN VIVO* DURING ADOLESCENCE

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SUMMARY

In the present study using magnetic resonance imaging (MRI), age changes in the morphology of the cerebral cortex, greatest in the frontal and parietal convexities, were observed during adolescence. Results suggest that increases in cerebrospinal fluid (CSF) within the sulci of these cortical regions accompany grey matter decreases. Smaller reductions in volume are also observed in subcortical grey matter nuclei. These apparent grey matter volume reductions presumably reflect processes of late brain maturation. The changes may be related to decreasing neural plasticity

INTRODUCTION

As brain systems mature, 'regressive events' (Cowan *et al.*, 1984) strongly influence their final form. Many more neurons are produced than will survive, and the elimination of neurons, which usually occurs early in development, may selectively reduce the neuronal populations in ways that increase the functional specificity and efficiency of the remaining neurons (Changeux and Danchin, 1976; Purves and Lichtman, 1980; Cowan *et al.*, 1984). In later phases of neural maturation, fewer neurons are lost, but substantial changes occur in synaptic density (Huttenlocher, 1979; Huttenlocher *et al.*, 1982). The selection of synapses is probably related to neural activity occurring in functionally maturing neuropil (Easter *et al.*, 1985). In human brain maturation, most neuronal cell death and much synaptic reorganization is thought to occur very early in development, either *in utero* or during the first or second post-natal years. Clinical magnetic resonance imaging (MRI) reveals dramatic developmental changes in the brains of infants, and is especially sensitive to the process of myelination (Holland *et al.*, 1986; Lee *et al.*, 1986; McArdle *et al.*, 1987*a*,*b*; Barkovich *et al.*, 1988; Martin *et al.*, 1988). But evidence exists that maturational changes continue into late childhood (Easter *et al.*, 1985). Autopsy studies have indicated that late cycles of myelination (Yakovlev and Lecours, 1967; Kinney *et al.*, 1988) and continuing changes in cortical synaptic density (Huttenlocher, 1979) occur throughout childhood. Evidence for late childhood changes in cerebral blood flow (Kennedy and Sokoloff, 1957; Kennedy *et al.*, 1970), the electroencephalogram of deep sleep (Feinberg, 1982) and cerebral metabolic rate (Chugani and Phelps, 1986; Chugani *et al.*, 1987) confirm that these changes are accompanied

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by functional alterations. Unfortunately, the neuropathological evidence for late childhood changes in humans is based on the examination of relatively few individuals aged between 7 and 16 yrs.

Using clinical MRI and semi-automated morphometry, Jernigan *et al.* (1990) examined brain structure in normal subjects ranging in age from 8 to 80 yrs. While some of the variability in morphologic measures across this age range was attributable to slow degenerative changes in older individuals, substantial age differences were apparent, especially in cortical structures, between the children and the adult subjects. Jernigan and Tallal (1990) reported that volumetric measures of the cortical grey matter from MR images revealed substantial differences between children and young adults, with the adults showing less cortical grey matter relative to cerebral size. However, the sample included no individuals aged between 10 and 26 yrs, thus little information was available about the timing of the changes. Also, since global cortical volume was measured, no information about the regional distribution of the changes was available, and questions remained about the degree to which late myelination of white matter might explain the apparent cortical reductions. Simultaneous increases in cerebrospinal fluid (CSF) and decreases in cortical grey matter suggested that cortical volume loss might be occurring. The brains of 39 normal children and young adults (23 males, 16 females, aged 8–35 yrs) have now been examined in greater detail with particular emphasis on regional changes in cortical morphology. Twenty of the subjects participating in the present study (9 children and 11 adults) were also examined in the earlier study.

METHOD

Subjects

Thirty-nine normal children and young adults (23 males, 16 females) were examined. Subjects 21 yrs of age and younger were recruited as normal controls for a large, multidisciplinary neurodevelopmental research centre. Subjects between 21 and 35 yrs of age participated as controls in neuropsychiatric studies. All subjects were screened by medical and psychiatric interviews (of parents or of subjects themselves) for evidence of significant disease (i.e. diabetes, heart disease), substance abuse, developmental intellectual abnormality, or psychiatric illness. All adult subjects were living independently in the community and were employed. Informed consent was obtained from all subjects and their parents when appropriate.

Imaging protocol

MR was performed with a 1.5 Tesla super-conducting magnet (Signa; General Electric, Milwaukee) at the UCSD/AMI Magnetic Resonance Institute. Two spatially registered images (Fig. 1) were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (TR = 2000 ms, TE = 25, 70 ms) to obtain images of the entire brain in the axial plane. Section thickness was 5 mm with a 2.5 mm gap between successive sections in all instances. A 256×256 matrix and 24 cm field of view were used. No sedation was administered for the examinations. For the following discussion of image analysis, the term pixel will be used to refer to a single picture element (or signal value) from the image matrix. The term voxel will be used to refer to the corresponding 3-dimensional volume from which the signal value for a pixel is taken.

Image analysis

The visual identification of cerebral structures in MR images is possible because of the tissue contrast between the grey matter structures and the surrounding white matter or CSF. However, measurements of volumes of cerebral structures must overcome several problems. First, because voxels at the edges of structures may contain mixtures of grey matter, white matter and CSF, sharply defined edges are not always

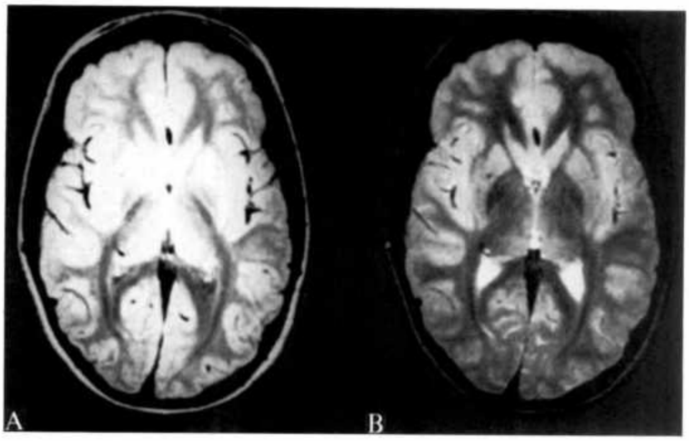

FIG. 1. Representative images from the standard protocol. A, axial section, SE 2000/25. B, axial section, SE 2000/70. Sections are 5 mm thick, matrix 256×256, with 2.5 mm gaps between images. A field of view of 24 cm was used.

present. This allows considerable scope for variability in subjective determinations of such boundaries (e.g. when tracing methods are used) leading to measurement unreliability in the computed volumes.

Visual identification of specific *cortical* structures on MRI presents additional challenges and depends upon the presence of visible gross morphologic features relative to which the boundaries of the cortical regions can be defined. Standard regional divisions for the cortex are based to a large extent on cortical gyral patterns, but the accurate localization of particular gyri or sulci, throughout a series of images, is often impossible. Furthermore, some boundaries, such as that between posterior temporal and inferior parietal cortex, are not clearly defined in gross morphological terms. Also, even when attempts are made to standardize head positioning, rotation of the head (relative to the standard plane) occurs in all three axes. This is especially likely when subjects are not sedated; they must be sufficiently comfortable in position to avoid movement during the imaging session. Careful inspection indicates that relatively small rotations substantially change the appearance of brain structures in the image plane, further complicating their visual identification; and, in addition, such rotations lead to spurious within-plane asymmetries of apparently comparable structures in the two hemispheres. Thus, manually tracing the structures in the sections where they are best visualized often leads to inaccurate volume and asymmetry assessments. The techniques described below were designed to address these problems.

To facilitate and standardize the determination of structural edges, our method involves a semi-automated classification of all pixels in the images on the basis of their signal characteristics on the two original images of each section. A detailed description of the pixel classification method has been reported (Jernigan *et al.*, 1990). Only a brief summary is provided here: for each axial brain section imaged, a computed matrix is produced. In this matrix, voxels are classified as most resembling (in signal strength) grey matter, white matter, CSF or signal hyperintensities (tissue abnormalities). The full series of axial images is analysed, beginning at the bottom of the cerebellar hemispheres and extending through the vertex.

Further manipulations to derive the specific structural measures for the studies reviewed here were then made using these 'pixel-classified' images. Trained operators, blind to subject age or gender, used a stylus-controlled cursor on the displayed images manually to separate cerebellar from cerebral areas, left from right hemispheres, and the cortical from subcortical regions.

Definition of subcortical structures

To delineate subcortical structures, the operators circumscribed pixels classified as subcortical grey matter that were visually determined to be in caudate nuclei, lenticular nuclei and diencephalic grey matter structures (including mammillary bodies, hypothalamic grey, septal nuclei and thalamus). They did not trace the edges of the structures, but designated polygons which included all grey matter pixels within the structures, and excluded those grey matter pixels associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as grey but clearly not in the structures, boundaries were manually constructed. Estimates of the volumes of the subcortical structures were made by summing the designated grey matter pixels across all sections.

Definition of cerebral (cortical) regions

To define anatomically consistent cerebral regions, a method was adopted for making subdivisions of the cerebrum relative to the centro-medial structural midline and two consistently identifiable points: the most anterior midline point in the genu and the most posterior midline point in the splenium of the corpus callosum. By calculating rotation angles using these landmarks, it was possible to perform a 3-dimensional rotation of the images, thus correcting each individual's image data for rotation out of the optimal imaging plane. Regions could then be constructed which resulted in highly consistent placement of regional boundaries relative to gross anatomical landmarks.

The two corpus callosum points were considered to lie in the true midsagittal plane. The orientation of this plane was then determined by computing a regression line through a series of visually selected brainstem midline points on different sections. The division of the cerebrum was based on two major planes (*see* Fig. 2): an *axial plane*, which is perpendicular in orientation to the midsagittal plane and passes through the two corpus callosum points, and a *coronal plane*, which is defined as perpendicular to the first plane and which passes through the midpoint between the two corpus callosum points. By computing new coordinates for each voxel relative to these planes, each is assigned to 1 of 4 zones: one, inferior to the axial plane and anterior to the coronal plane (IA); a second, inferior to the axial plane and posterior to

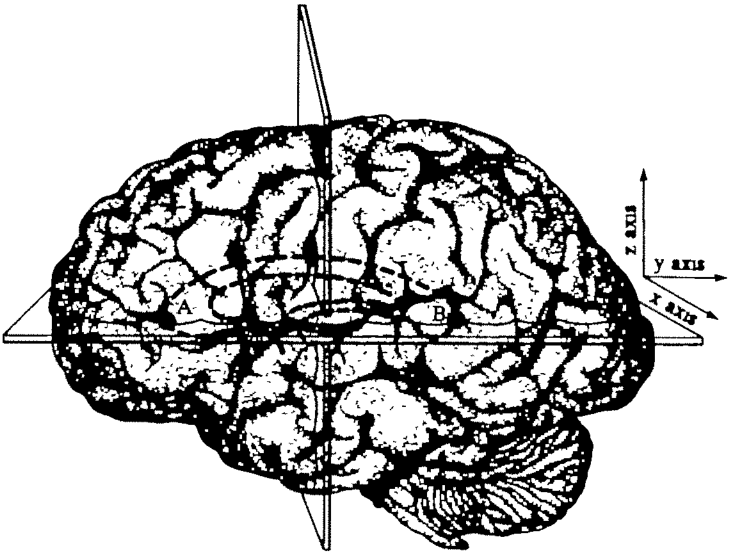

FIG. 2. Cerebral regions are defined as follows. Points A and B in the corpus callosum, shown above, are the most anterior midline point in the genu, and the most posterior midline point in the splenium, respectively An axial plane passing through these two points is defined, as shown, perpendicular to the midsagittal plane. A coronal plane is defined perpendicular to the axial plane and passing through the midpoint between points A and B. Thus 4 cerebral zones are defined. inferior anterior, inferior posterior, superior anterior and superior posterior. Anterior temporal, orbito-frontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone contains primarily parietal and superior occipital cortex.

the coronal plane (IP): a third, superior to the axial plane and anterior to the coronal plane (SA); and a fourth, superior to the axial plane and posterior to the coronal plane (SP). Again, these defined planes are independent of the image plane, as a 3-dimensional rotation is first applied based on the positions of the landmarks described above. Anterior temporal, orbito-frontal, and some dorsolateral and mesial frontal cortex lie in the inferior anterior zone. Posterior temporal and inferior occipital cortex fall in the inferior posterior zone. Most of the remaining parts of the frontal lobe fall into the superior anterior zone, and the superior posterior zone contains primarily parietal and a small portion of the superior occipital cortex.

The fully processed images are illustrated in Fig. 3. The colour coding for different pixel classes is described in the figure legend. The red line running through each section indicates the position of the coronal dividing plane. Because this plane passes through the diencephalic grey matter regions and divides the functionally distinct hypothalamic and septal structures (lying anteriorly) from the bulk of the thalamus

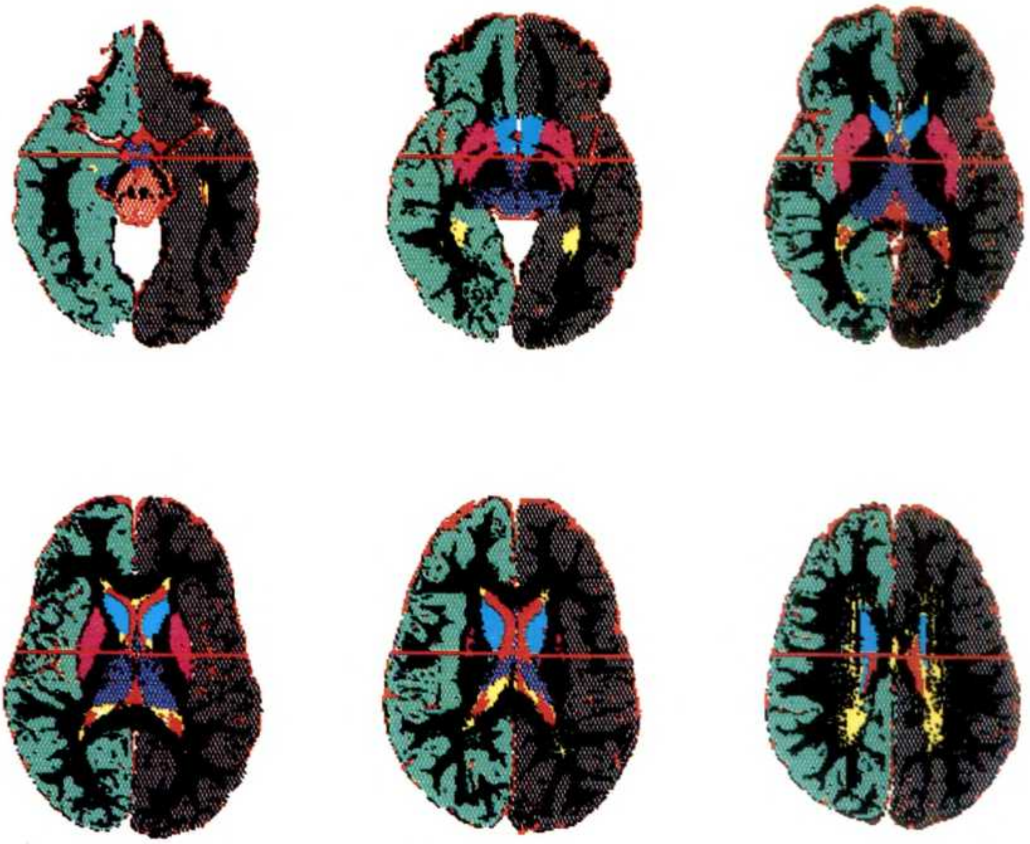

FIG. 3. Representative fully processed images. The different pixel classes are colour coded as follows: right-hemisphere cortical grey matter is green, and left-hemisphere cortical grey matter is grey. Diencephalic areas are purple, caudate nuclei are blue and lenticular nuclei are magenta. The red line running through each section indicates the position of the coronal dividing plane. The sections on the top row are below and the sections on the bottom row above the axial dividing plane. This set of images was chosen because the imaging plane is parallel to the axial dividing plane and virtually no rotation of the head in the coronal or sagittal planes occurred. Note that, due to 3-dimensional image rotation, in typical sets of images, the separation of inferior from superior zones would not coincide with a section boundary, but would occur within a section.

(lying posteriorly), the corresponding anterior and posterior diencephalic volumes were computed separately. It should be noted that areas within the lenticular nucleus containing significant iron deposits, particularly in globus pallidus, do not meet the signal criteria for grey matter and are thus not included in this region. Fluid and white matter are shown in red and black, respectively; however, subcortical and cortical fluid are measured separately.

The cortical grey matter voxels and the cortical sulcal CSF voxels within each of the 4 zones were summed separately, as were the totals of all intracranial voxels (including brain and CSF) within each zone.

Ten full sets of images were analysed twice several weeks apart. The repeat analyses were conducted blind and completely independently of the first analyses. Thus, reliability of the method could be determined for the volume measures. Reliability coefficients (Pearson r) were as follows: supratentorial volume, 0.99; infratentorial volume, 0.99; ventricular CSF, 0.99; cortical CSF, 0.99; cortical grey matter, 0.88; caudate, 0.93; diencephalon, 0.87; and lenticular nuclei, 0.73.

Statistical analysis

The statistical analyses were descriptive. The magnitude of the independent effects of age and gender on the morphologic variables were estimated separately using multiple linear regression analyses. Effects of these variables on the cortical grey matter and CSF volumes were estimated, adjusting for variation due to the size of the cranial regions from which the volumes were taken. This was accomplished by entering the regional cranial volumes in the multiple regressions as additional predictors, so that any observed effects of age or gender could be assumed to be independent of (not attributable to) variation in region size. Similarly, the age and gender effects on the subcortical grey matter volumes were estimated after removing variance due to total supratentorial cranial volume. In these analyses the magnitude of the independent effect of a variable is reflected in that variable's regression coefficient in the presence of the other predictors. Probabilities given for each coefficient estimate the likelihood that such a value would occur by chance when in fact the predictor is unrelated to the criterion variable.

RESULTS

In preliminary analyses, the supratentorial cranial volume and the volumes of the 4 subregions were examined for evidence of continuing growth during this age range. The results are presented in Table 1. The supratentorial volume is considerably smaller in female subjects ($P = 0.001$). Controlling for the gender effect, the age increase is small ($P = 0.08$). Examination of the results for the different regions, however, suggests that some continuing growth may take place in the superior frontal region ($P = 0.009$). The gender effect is present and comparable in size in inferior cerebral regions, somewhat less pronounced in the superior posterior region, and not observed in the superior anterior region.

TABLE. 1. REGRESSION ANALYSES ON CRANIAL VOLUMES

	Effect of gender		*Effect of age*	
	β	P	β	P
Total supratentorial cranium	−0.483	0.001	0.252	0.076
Cranial regions				
Inferior anterior	−0.492	0.002	−0.096	0.519
Inferior posterior	−0.468	0.003	−0.010	0.948
Superior anterior	−0.185	0.221	0.408	0.009
Superior posterior	−0.365	0.018	0.281	0.064

β = standardized regression coefficient; P = significance level for β.

The analyses of the cortical grey matter volumes are summarized in Table 2. In all 4 regions the cortical grey matter volume is, predictably, highly associated with the volume of the total cerebral region from which it was measured. After adjusting for regional volume differences, however, no gender effect is observed for any cortical volume. There is no evidence for age-related change in the cortical volumes from either of the 2 inferior cortical regions; however, substantial age decreases are measured in both the superior anterior ($P < 0.001$) and superior posterior ($P < 0.001$) regions.

TABLE. 2. REGRESSION ANALYSES FOR REGIONAL CORTICAL GREY MATTER VOLUMES

	Effect of regional volume		*Effect of gender*		*Effect of age*	
	β	P	β	P	β	P
Cortical region						
Inferior anterior	0.909	0.000	0.064	0.495	0.026	0.754
Inferior posterior	0.779	0.000	0.045	0.722	−0.136	0.227
Superior anterior	0.937	0.000	0.060	0.513	−0.593	0.000
Superior posterior	0.830	0.000	0.010	0.925	−0.559	0.000

β = standardized regression coefficient; P = significance level for β.

The results of similar analyses for the cortical sulcal CSF volumes in these regions are presented in Table 3. Again, the volumes are corrected for regional volume, and again no independent effects of gender on the volumes are observed. However, definite age-related increases are observed in the volumes computed from both of the superior cortical regions ($P < 0.001$ for both regions). A scatterplot illustrating the age-related changes in the superior cortex is shown in Fig. 4. For this figure, a superior cortical grey matter measure was computed by combining the anterior and posterior cortical volumes. As shown in the regression analyses, this volume was highly positively correlated with the total superior region volume. This correlation yields a formula for predicting the superior cortical volume from the regional volume. To adjust for the irrelevant variability in regional volume, a residual cortical volume was computed. That is, the volume was expressed as a deviation from the cortical volume predicted from the total regional volume. Thus the variability in this new cortical volume measure is

TABLE. 3. REGRESSION ANALYSES FOR REGIONAL CORTICAL CSF VOLUMES

	Effect of regional volume		*Effect of gender*		*Effect of age*	
	β	P	β	P	β	P
Cortical region						
Inferior posterior	0.309	0.103	0.248	0.193	0.126	0.448
Inferior posterior	0.303	0.106	0.276	0.143	0.048	0.771
Superior anterior	−0.031	0.840	0.253	0.077	0.606	0.000
Superior posterior	−0.021	0.897	−0.017	0.911	0.582	0.000

β = standardized regression coefficient; P = significance level for β.

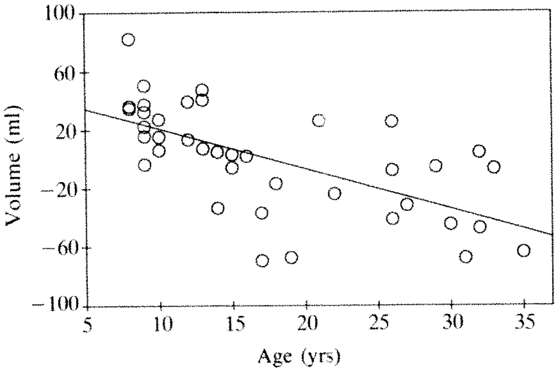

FIG. 4. Scatterplot of superior cortical grey matter volumes across age. The measure is a residual score after adjustment for total volume of the 2 superior supratentorial regions. The formula, taken from a regression of superior regional volume on superior cortical grey volume, is as follows: residual superior cortical volume = superior cortical grey volume −[151.52+(0.00196×superior regional volume)]. Values decrease with increasing age.

unrelated to regional volume. Inspection of Fig. 4 shows that the measure is strongly related to age.

The analyses of subcortical grey matter volumes and ventricular CSF are summarized in Table 4. After adjusting for the size of the supratentorial cranium, no gender effects are observed. There is evidence for reduction with increasing age in both basal ganglia measures ($P = 0.01$ for caudate, $P = 0.000$ for lenticular nucleus), and in the posterior diencephalic measure, which includes mostly thalamus ($P = 0.008$). Surprisingly, there is an apparent increase with age in the volume of the anterior diencephalic grey matter (consisting of hypothalamic grey matter, septal nuclei and some very anterior parts of the thalamus). The volume of ventricular CSF increases across this age range ($P = 0.001$).

TABLE 4. REGRESSION ANALYSES FOR SUBCORTICAL STRUCTURES

	Effect of cranial size		*Effect of Gender*		*Effect of age*	
	β	P	β	P	β	P
Caudate	0.623	0.001	0.143	0.384	−0.402	0.010
Lenticular nucleus	0.321	0.066	−0.121	0.460	−0.563	0.000
Anterior diencephalic grey	0.070	0.700	0.210	0.233	0.470	0.005
Posterior diencephalic grey	0.310	0.099	−0.075	0.669	−0.447	0.008
Ventricular CSF	0.042	0.815	0.158	0.362	0.494	0.003

β = standardized regression coefficient; P = significance level for β.

Finally, the correlations between the regional cortical grey matter and CSF measures, and between the subcortical grey matter measures and the ventricular CSF measure are summarized in Table 5A and 5B respectively. The coefficients are partial correlations controlling for regional volume (for the cortical measures) or the supratentorial volume (for subcortical measures). There are moderate correlations between superior cortical

TABLE 5A PARTIAL CORRELATIONS OF REGIONAL CORTICAL GREY MATTER VOLUMES WITH REGIONAL CORTICAL CSF VOLUMES CONTROLLING FOR REGIONAL VOLUMES

	r	P
Region		
Inferior anterior	−0 08	0.63
Inferior posterior	−0 21	0.20
Superior anterior	−0.56	0.00
Superior posterior	−0.54	0.00

TABLE 5B PARTIAL CORRELATIONS OF SUBCORTICAL GREY MATTER VOLUMES WITH VENTRICULAR CSF VOLUME CONTROLLING FOR SUPRATENTORIAL CRANIAL VOLUME

	r	P
Caudate	−0.52	0.00
Lenticular	−0.40	0.01
Anterior diencephalon	0.15	0.37
Posterior diencephalon	−0.37	0 02

r = partial correlation coefficient; *P* = significance level for *r*

grey volumes and the CSF volumes from the adjacent sulci, but no correlation for the inferior zones. Also, the peri-ventricular subcortical structural volumes show some degree of correlation with the ventricular measure.

Estimated volumes for the measured brain structures are given in Table 6.

DISCUSSION

Jernigan and Tallal (1990) reported a decline in the cortical grey matter proportion in adults relative to children. Expressing the cortical volume as a proportion, either of the cranial volume or of a regional volume, is a method often used to improve the sensitivity of the cortical measure by removing the effects of irrelevant variation in head size from one subject to the next. A decreasing proportion is interpreted as evidence for thinning of the cortex. However, such a proportion will decrease with age even though the cortical volume remains constant, if the cranial or regional volume is increasing. The results of the present study suggest that an increase in the cranial volume may occur over this age range, especially in the superior prefrontal region. This small increase is consistent with evidence that the cranial sutures do not completely fuse until after 30 yrs of age (Hodges, 1971), and with radiological observations of increases in cerebral size during late childhood (Ethier, 1971). Given a cranial volume increase, the cortical proportion may be an inappropriate measure of cortical thickness. The multiple regression method used here provides estimates of the independent effects of brain size differences, gender and age on the cortical volumes. Thus, the significant age-decreases reported here are not due to increasing brain size. They occur because (statistically) an older person with a given brain size has less cortical grey matter than a younger person with the same brain size.

TABLE 6. MEAN (STANDARD DEVIATION) VOLUMES FOR ANATOMICAL MEASURES IN MILLILITRES

	Mean (SD)
Total Supratentorial Cranium	1296.63 (122.61)
Cranial regions	
Inferior anterior	201.13 (26.08)
Inferior posterior	307.97 (37.66)
Superior anterior	319.30 (44.05)
Superior posterior	468.38 (56.17)
Regional cortical grey matter volumes	
Inferior anterior	105.20 (15.15)
Inferior posterior	150.72 (28.03)
Superior anterior	155.78 (20.35)
Superior posterior	229.37 (29.72)
Regional cortical CSF volumes	
Inferior anterior	17.12 (4.37)
Inferior posterior	16.52 (4.34)
Superior anterior	27.09 (9.63)
Superior posterior	35.66 (13.40)
Subcortical structures	
Caudate	13.10 (2.03)
Lenticular nucleus	14.57 (2.26)
Anterior diencephalic grey	2.59 (0.73)
Posterior diencephalic grey	13.89 (2.75)
Ventricular CSF	16.70 (5.36)

The present results suggest that the changes are localized in the superior cortical regions (comprised mostly of the frontal and parietal convexities). No evidence was found for significant change in the inferior cortical regions. Yakovlev and Lecours (1967) described continuing myelination after the first decade in the intracortical neuropil of what they referred to as the supralimbic areas. These regions make up a considerably larger proportion of our superior than our inferior regions. Thus, apparent cortical thinning in these regions could be due to late peripheral arborization of myelin. If, however, the cortical changes observed here were simply due to decreases in signal values within pixels near the edge of the cortical rim (associated with myelination), then no concurrent increases in CSF overlying these cortical regions would be expected. However, the regional pattern of age correlations for cortical CSF closely resembles that for cortical grey matter. The grey matter/CSF correlations show that the apparent cortical decreases are associated with visually subtle, but closely related, increases in adjacent sulcal CSF. This suggests that loss of constituents of the cortical neuropil accompanies the apparent cortical thinning, some of which may be due to myelination. An alternate explanation is that maturational changes coinciding with late myelination in these areas are associated with other biochemical processes in the cortex leading to the local accumulation of CSF.

Secondary analyses suggest that morphologic changes in this age range are not confined to cortical structures. The posterior diencephalic measure, consisting mostly of the thalamus, appears to undergo a subtle reduction in volume. Basal ganglia structures also appear to decrease in volume. However, because increasing iron deposition over this age range would reduce the apparent volume of these structures using the present methods, these observations must be interpreted with caution. Such an explanation is especially likely for the changes observed in lenticular nucleus, where accumulation of iron has been amply demonstrated (Drayer *et al.*, 1986; Drayer, 1988). It is less likely to account for the caudate reductions. Furthermore, the fact that increases in CSF in the adjacent ventricles occur in association with the apparent reductions in caudate and thalamus, strengthens the argument for actual volume reductions of these structures.

The increase in the anterior diencephalic structures is entirely unexpected. The region measured is comprised of a set of small structures difficult to separate at the resolution achieved in the present images. Interpretation of increasing volume in these structures during adolescence should await replication. It is of interest, however, that animal studies have shown post-natal anatomic variation induced by gonadal steroids (*see* Arnold and Gorski, 1984, for review); and that receptors for these hormones are concentrated in some of the structures within our anterior diencephalic region, such as hypothalamic nuclei and septum (Stumpf and Sar, 1978; Rainbow *et al.*, 1982). Two recent MR studies (Hayakawa *et al.*, 1989; Elster *et al.*, 1990) have provided evidence that a growth spurt occurs in the pituitary gland at approximately the same age that we observe increasing anterior diencephalic volume. Taken together, these results suggest that pubertal hormonal changes may be accompanied by related brain structural alterations.

Huttenlocher (1979) has observed reductions in synaptic density in human frontal cortex during roughly the same age range as the changes reported here. It is possible that both observations reflect maturation of specific cortical structures during adolescence. In the present study, no change is observed within this age range in inferior cortical areas, suggesting regional variation in human cortical maturation. Other evidence for regional variation comes from Huttenlocher *et al.* (1982, 1987) who have suggested that changes in synaptic density in the occipital lobe are completed earlier than those in the frontal cortex. This appears to be in conflict with the findings in monkeys (Rakic *et al.*, 1986) which indicate that synaptic density declines in diverse cortical regions simultaneously.

Structural changes within these cortical regions could play an important role in such functional changes during adolescence as those that have been observed with sleep EEG (Feinberg *et al.*, 1977) and brain metabolism (Kennedy and Sokoloff, 1957; Chugani and Phelps, 1986; Chugani *et al.*, 1987). Purves (1988) has suggested that modification of central connectivity may be necessary during the rapid somatic growth of adolescence, and thus long-persisting neural plasticity may be needed to accommodate these changes.

Morphologic changes observed in the present study may also relate to pubertal alterations of higher cognitive and affective functions, or to the decrease in cortical plasticity thought to occur during late childhood and adolescence. Finally, they may be relevant in the pathogenesis of major psychiatric disorders, such as schizophrenia, which have a characteristic onset in late adolescence (Feinberg, 1982, 1982/1983, 1987). These speculations suggest hypotheses that may be testable *in vivo* in behavioural studies using MRI and morphometric techniques.

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REFERENCES

ARNOLD AP, GORSKI RA (1984) Gonadal steroid induction of structural sex differences in the central nervous system. *Annual Review of Neuroscience*, **7**, 413–442.

BARKOVICH AJ, KJOS BO, JACKSON DE, NORMAN D (1988) Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T. *Radiology*, **166**, 173–180.

CHANGEUX J-P, DANCHIN A (1976) Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. *Nature, London*, **264**, 705–712.

CHUGANI HT, PHELPS ME (1986) Maturational changes in cerebral function in infants determined by ^{18}FDG positron emission tomography. *Science*, **231**, 840–843.

CHUGANI HT, PHELPS ME, MAZZIOTTA JC (1987) Positron emission tomography study of human brain functional development. *Annals of Neurology*, **22**, 487–497.

COWAN WM, FAWCETT JW, O'LEARY DDM, STANFIELD BB (1984) Regressive events in neurogenesis. *Science*, **225**, 1258–1265.

DRAYER BP (1988) Imaging of the aging brain: Part I. Normal findings. *Radiology*, **166**, 785–796.

DRAYER B, BURGER P, DARWIN R, RIEDERER S, HERFKENS R, JOHNSON GA (1986) MRI of brain iron. *American Journal of Roentgenology*, **147**, 103–110.

EASTER SS, PURVES D, RAKIC P, SPITZER NC (1985) The changing view of neural specificity. *Science*, **230**, 507–511.

ELSTER AD, CHEN MYM, WILLIAMS DW, KEY LL (1990) Pituitary gland: MR imaging of physiologic hypertrophy in adolescence. *Radiology*, **174**, 681–685.

ETHIER R (1971) Thickness and texture. In: *Radiology of the Skull and Brain. The Skull.* Volume 1, Book 1. Edited by T. H. Newton and D. G. Potts. St. Louis: C. V. Mosby, pp. 154–215.

FEINBERG I (1982) Schizophrenia and late maturational brain changes in man. *Psychopharmacology Bulletin*, **18**, Number 3, 29–31.

FEINBERG I (1982/1983) Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, **17**, 319–334.

FEINBERG I (1987) Adolescence and mental illness. *Science*, **236**, 507–508.

FEINBERG I, HIBI S, CARLSON VR (1977) Changes in EEG amplitude during sleep with age In: *The Aging Brain and Senile Dementia*. Edited by K. Nandy and I. Sherwin. New York: Plenum Press, pp. 85–98.

HAYAKAWA K, KONISHI Y, MATSUDA T, KURIYAMA M, KONISHI K, YAMASHITA K *et al.* (1989) Development and aging of brain midline structures: assessment with MR imaging. *Radiology*, **172**, 171–177.

HODGES FJ (1971) Alterations in the skull with aging. In: *Radiology of the Skull and Brain. The Skull.* Volume 1, Book 1. Edited by T. H. Newton and D. G. Potts. St. Louis: C. V. Mosby, pp.132–138.

HOLLAND BA, HAAS DK, NORMAN D, BRANT-ZAWADZK M, NEWTON TH (1986) MRI of normal brain maturation. *American Journal of Neuroradiology*, **7**, 201–208.

HUTTENLOCHER PR (1979) Synaptic density in human frontal cortex–developmental changes and effects of aging. *Brain Research, Amsterdam*, **163**, 195–205.

HUTTENLOCHER PR, DE COURTEN C, GAREY LJ, VAN DER LOOS H (1982) Synaptogenesis in human visual cortex–evidence for synapse elimination during normal development. *Neuroscience Letters*, **33**, 247–252.

HUTTENLOCHER PR, DE COURTEN C (1987) The development of synapses in striate cortex of man. *Human Neurobiology*, **6**, 1–9.

JERNIGAN TL, PRESS GA, HESSELINK JR (1990) Methods for measuring brain morphologic features on magnetic resonance images: validation and normal aging. *Archives of Neurology, Chicago*, **47**, 27–32.

JERNIGAN TL, TALLAL P (1990) Late childhood changes in brain morphology observable with MRI. *Developmental Medicine and Child Neurology*, **32**, 379–385.

KENNEDY C, SOKOLOFF L (1957) An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and cerebral metabolic rate in childhood. *Journal of Clinical Investigation*, **36**, 1130–1137.

KENNEDY C, GRAVE GD, JEHLE JW, SOKOLOFF L (1970) Blood flow to the white matter during maturation of the brain. *Neurology, Minneapolis*, **20**, 613–618.

KINNEY HC, BRODY BA, KLOMAN AS, GILLES FH (1988) Sequence of central nervous system myelination in human infancy: II. Patterns of myelination in autopsied infants. *Journal of Neuropathology and Experimental Neurology*, **47**, 217–234.

LEE BCP, LIPPER E, NASS R, EHRLICH ME, DE CICCIO-BLOOM E, AULD PAM (1986) MRI of the central nervous system in neonates and young children. *American Journal of Neuroradiology*, **7**, 605–616.

MCARDLE CB, RICHARDSON CJ, NICHOLAS DA, MIRFAKHRAEE M, HAYDEN CK, AMPARO EG (1987*a*) Developmental features of the neonatal brain: MR imaging: Part I. Gray-white matter differentiation and myelination. *Radiology*, **162**, 223–229.

MCARDLE CB, RICHARDSON CJ, NICHOLAS DA, MIRFAKHRAEE M, HAYDEN CK, AMPARO EG (1987*b*) Developmental features of the neonatal brain: MR imaging: Part II. Ventricular size and extracerebral space. *Radiology*, **162**, 230–234.

MARTIN E, KIKINIS R, ZUERRER M, BOESCH C, BRINER J, KEWITZ G *et al.* (1988) Developmental stages of human brain: an MR study. *Journal of Computer Assisted Tomography*, **12**, 917–922.

PURVES D (1988) *Body and Brain: A Trophic Theory of Neural Connections*. Cambridge, MA and London: Harvard University Press.

PURVES D, LICHTMAN JW (1980) Elimination of synapses in the developing nervous system. *Science*, **210**, 153–157.

RAINBOW TC, PARSONS B, MACLUSKY NJ, MCEWEN BS (1982) Estradiol receptor levels in rat hypothalamic and limbic nuclei. *Journal of Neuroscience*, **2**, 1439–1445.

RAKIC P, BOURGEOIS J-P, ECKENHOFF MF, ZECEVIC N, GOLDMAN-RAKIC PS (1986) Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. *Science*, **232**, 232–235.

STUMPF WE, SAR M (1978) Anatomical distribution of estrogen, androgen, progestin, corticosteroid and thyroid hormone target sites in the brain of mammals: phylogeny and ontogeny. *American Zoologist*, **18**, 435–445.

YAKOVLEV PI, LECOURS A-R (1967) The myelogenetic cycles of regional maturation of the brain. In: *Regional Development of the Brain in Early Life*. Edited by A. Minkowski. Oxford: Blackwell Scientific, pp. 3–70.

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MEDIAL VS LATERAL FRONTAL LOBE LESIONS AND DIFFERENTIAL IMPAIRMENT OF CENTRAL-GAZE FIXATION MAINTENANCE IN MAN

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SUMMARY

The ability to maintain central-gaze fixation was studied in 35 patients with unilateral frontal lobe lesions. The stability of central-gaze fixation was tested in 2 oculomotor tasks requiring the suppression of reflexive saccades triggered by the sudden appearance of novel, peripheral visual stimuli. In the first task ('Instructed'), maintenance of gaze fixation was based on verbal instruction, whereas, in the second task ('Non-instructed'), it was based upon a foveating mechanism maintained by sensory stimulation during the performance of a categorization task. Patients with frontal lobe lesions were classified into 3 groups: a ventrolateral ($n = 18$), a dorsolateral ($n = 10$) and a medial ($n = 7$) group. The control group consisted of 20 healthy subjects. In the Non-instructed task, no group differences were found in the rate of reflexive saccades. Thus, lesions of the frontal lobe did not affect reactivity to extraneous stimuli *per se*. The only exception to this rule was the group of patients with ventrolateral lesions in the left frontal lobe, in which a higher number of reflexive saccades directed to the contralateral hemifield was observed. In the Instructed task, 2 different patterns of deficit in suppression of reflexive saccades were found. First, a bidirectional deficit was noted in the ventrolateral group, which might be attributed to an impairment in either maintaining a selected program of behaviour 'on-line' or suppressing inappropriate alternatives interfering with that program. Second, a unidirectional deficit in voluntary suppression of reflexive saccades triggered from within the contralateral hemifield was observed in the medial group. It is suggested that this type of deficit may reflect malfunctioning of the supplementary motor area—anterior cingulate system involved in the suppression of externally triggered interfering programs. Finally, no significant impairment was found in the dorsolateral group.

INTRODUCTION

Suppression of externally triggered interfering programs is a condition for maintaining goal-directed, purposeful behaviour. The frontal cortex has been considered to be involved in this type of regulation for many decades (e.g. Bianchi, 1922; Luria, 1980; Shallice, 1982). In the present investigation, the effect of lesions to the frontal lobe upon the ability to maintain a verbally instructed central-gaze fixation was examined in a task requiring suppression of reflexive saccades triggered by the sudden appearance of novel peripheral stimuli.

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The main aim of the present study was two-fold. First, we wanted to demonstrate functional heterogeneity within the frontal cortex as related to specific aspects of oculomotor control. In the present study, we were able to compare the effect of unilateral lesions confined to the ventrolateral, medial, or dorsolateral frontal cortex. Secondly, we tried to dissociate the specific effect of frontal lesions on the maintenance of verbally instructed gaze fixation from the more general one related to changes in reactivity to extraneous stimuli. To accomplish this we have used a control task in which central-gaze fixation was based upon the operation of a more automatic mechanism not requiring voluntary control of gaze to the same extent as in our first task.

SUBJECTS

Sixty-six adult patients with frontal lobe lesions of varying aetiology were studied. All but 3 patients underwent a neurosurgical operation and were examined from 5 mths to 6 yrs following operation. Twenty-four patients were excluded from the study because of the absence of a selective cortical lesion or because of the existence of multiple brain lesions as demonstrated by a CT scan; in addition, 4 patients were excluded because of the absence of a recent CT scan, and 3 patients were not able to finish the experimental tasks. Twenty normal control subjects were also tested in this experiment. Informed consent was obtained from all subjects.

For the remaining 35 patients, recent CT scans were evaluated by the second author (M.K.). The lesions were marked onto the corresponding drawings of a CT brain atlas and the patients were classified into 3 groups: a dorsolateral (n = 10), a ventrolateral (n = 18) and a medial (n = 7) group. In Fig. 1, schematic density maps of the lateral and the medial extent of the lesions (A), and the horizontal extent of lesions at the level of the highest density (B) are shown.

Table 1 shows the number, age, sex, handedness, aetiology, duration of pathology and site of lesion for each group of subjects, as well as scores obtained on the 'Mini Mental State' examination.

METHODS

All subjects were tested on 2 oculomotor tasks (Instructed and Non-instructed), as well as a modified version of the Wisconsin Card Sorting Test and the Word Fluency Test.

Oculomotor tasks

Apparatus and stimuli. Visual stimuli were presented on a computer screen. The central stimulus (composed of about 200 pixels) emerged gradually inside a frame in the centre of the screen over a period of 10 s (trial duration). Two different types of the central stimuli were used. Meaningful, complex stimuli consisting of drawings of animals and meaningless stimuli consisting of random pixel patterns. Peripheral stimuli, 'U'- and 'F'-like forms, were displayed on the left or the right side of the central stimulus. The central (frame) and the peripheral stimulus size was 2.7 by 2.0 angular degrees and 0.4 by 0.7 degrees, respectively. The distance from the central to the peripheral stimulus was 4.2 degrees (centre to centre).

Horizontal eye movements were recorded by means of DC electro-oculography (EOG) and digitized at a sampling interval of 10 ms. The occurrence of reflexive saccades, saccade latency and time of gaze fixation of the peripheral stimulus were assessed visually from 2-s EOG recordings beginning with the peripheral stimulus onset.

Procedure. In the Instructed task, meaningless central stimuli were presented. The subjects were instructed that their only task was to gaze at the central stimulus and not outside the frame for the duration of its presence. No manual motor reaction was required to this stimulus.

In the Non-instructed task, meaningful central stimuli (i.e. shapes of animals) were used. The task of the subject was to categorize the stimulus items into wild and domesticated animals. The subject was told to place his right hand on the computer keyboard and to press, with the second or the third finger, the appropriate response key as soon as he decided the category of the animal. Verbal instruction concerned the description of the categorization task only and did not concern gaze direction explicitly.

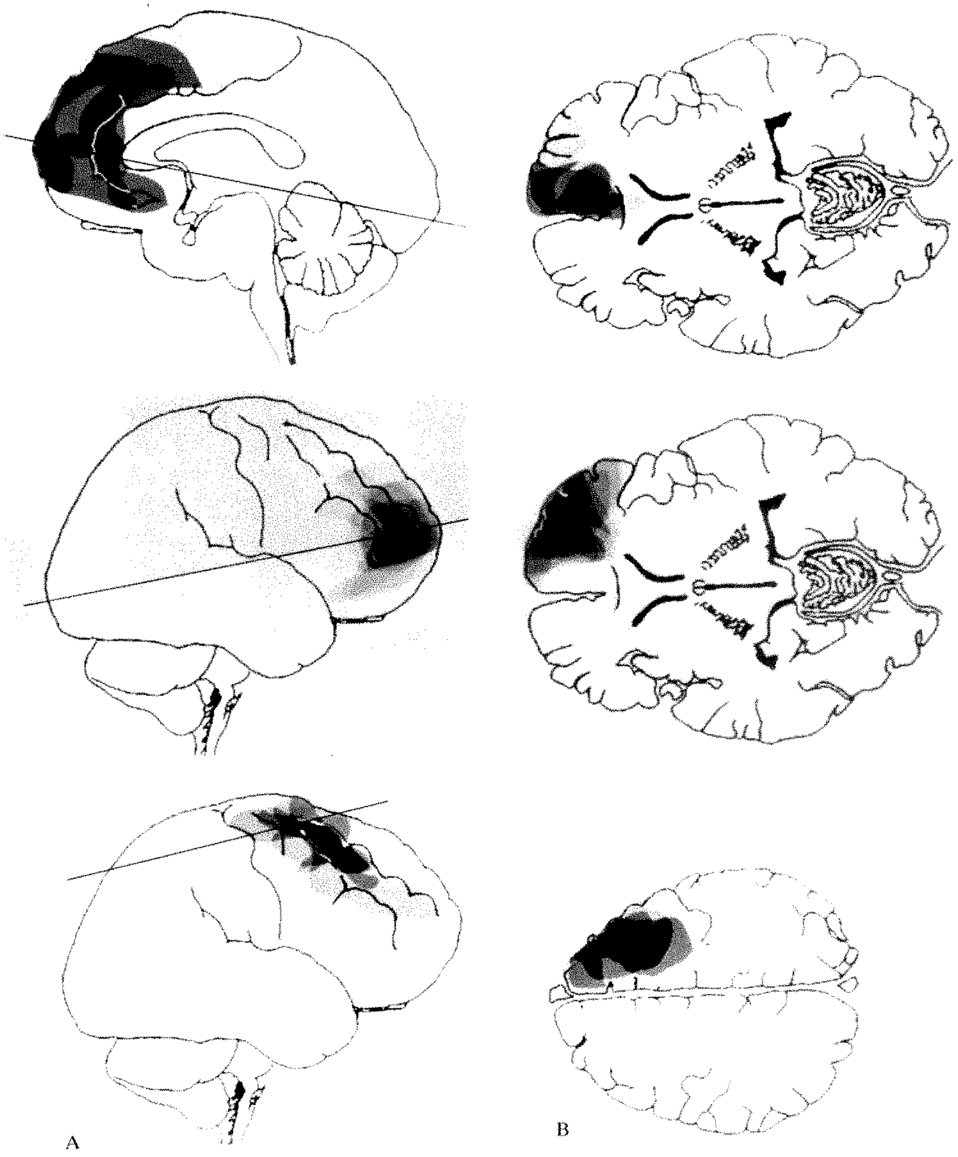

FIG. 1. Density maps of the lesions in the frontal lobe groups. The oblique lines on the lateral or medial views of hemisphere, on the left side of the figure (A), show the level of the horizontal density maps displayed on the right (B). The density maps were constructed by superimposing the schematic drawings of the CT scans of the patients in each group.

Peripheral stimuli were displayed during the central stimulus presentation in both tasks. The time delay from the beginning of the trial to the peripheral stimulus onset was 2 s, and its duration 0.5 s. Peripheral stimuli were presented in 11 trials chosen randomly from the total of 40 trials that constituted each task. The type and position of peripheral stimuli used in those 11 trials varied randomly to prevent habituation. For technical reasons, 6 peripheral stimuli were presented in the left hemifield and only 5 in the right hemifield. The subjects were not told in advance that peripheral stimuli were to appear during the test.

TABLE 1. DESCRIPTION OF SUBJECTS

	Group			
	Dorsolateral	*Ventrolateral*	*Medial*	*Control*
Number of subjects	10	18	7	20
Sex (Female, Male)	3F, 7M	3F, 15M	0F, 7M	10F, 10M
Age (yrs)	47 ± 10	43 ± 17	49 ± 10	40 ± 12
Pathology duration (mths)	30 ± 34	35 ± 55	24 ± 14	
Side of lesion				
Right	3	9	3	
Left	7	9	4	
Aetiology				
Haemorrhage	1	10	2	
Ischaemia	2	0	0	
Meningioma	4	5	1	
Abscess	1	2	0	
Cyst	2	0	0	
ACoA aneurysm*	0	0	4	
ACM aneurysm*	0	1	0	
Mini Mental State (Score)	22.5 ± 2.2	23.3 ± 1.7	22.9 ± 2.0	
Handedness				
Right-handers	9	18	5	18
Left-handers	0	0	0	0
Ambidextrous	1	0	2	2

*ACoA = arteria communicans anterior; ACM = arteria cerebri media.

The order of administration of the 2 oculomotor tasks was counterbalanced across subjects. Initiation of the trials was self-paced. When the second task had been finished, the subject was asked whether anything had occurred outside the frame during testing. If the appearance of letters was reported, the subjects were asked whether they had made an eye movement towards these stimuli. The subjects were also asked whether eye movements to the peripheral stimuli were made intentionally or not.

Word fluency task (WF)

The oral version of the WF was administered. The score was the total number of words beginning with the 3 stimulus letters, B, M and J, produced within 1 min for each letter. The scores for the first and the second 30 s of the test were analysed separately.

A modified version of the Wisconsin Card Sorting Test (WCST)

The WCST was administered and scored according to Nelson's (1976) procedure. Scoring was based on the number of sorting principles (categories) derived by the subject (Cat), the number of total errors made (TE), the number of unique errors (U) and the number of perseverative errors (PE), defined in terms of the inappropriate continuation of an earlier correct principle. Relative number of PE (PE/TE × 100) was also calculated.

Mini Mental State examination (MMS)

A modified version of the MMS (Folstein *et al.*, 1975) was administered, the maximum score being 25. The Place Orientation item was omitted.

Handedness

Measurement of handedness was based on only 12 of the 13 questionnaire items (Chapman and Chapman, 1987). Question 13 (On which shoulder do you rest a bat before swinging?) was omitted because it was considered inappropriate for our subject population. Scores ranged from 12 to 16, 17 to 29 and 30 to 36 for right-handed subjects, ambidextrous and left-handed subjects respectively.

The test battery was administered in the following fixed order: oculomotor tasks (Instructed and

Non-instructed, being counterbalanced across subjects), WCST, MMS, WF and handedness questionnaire. The session lasted from 90 to 120 min. Clinical neurological assessment of the patients was performed on the same day by trained neurologists.

RESULTS

Oculomotor tasks

Overall reflexive saccade rate. Fig. 2 shows the overall rate of reflexive saccadic eye movements for each group of subjects in both tasks. In the Non-instructed task, a one-way ANOVA yielded no significant group differences [F(3,49) = 0.9, n.s.]. On average, reflexive saccades were made in 51 ± 28% of trials with peripheral stimulus presentation. However, there was marked inter-individual variability in the saccade rate in this task. In the Instructed task, a one-way ANOVA revealed significant group differences [F(3,51) = 7.3, $P < 0.001$]. The highest saccade rate was found in the medial group followed by the ventrolateral, the dorsolateral and the control groups. The control subjects had no difficulties in suppressing reflexive saccades to almost all of the peripheral stimuli in this task. Paired comparison of the saccade rate between the control and each one of the patient groups was performed separately using an analysis of variance for two-factor experiments with repeated measurements on one factor. The values obtained are shown in Table 2. A significant main effect of task has been revealed in all of these paired comparisons. The main effect of group has been found in all but control vs dorsolateral group comparison. The only significant interaction was found in the control vs medial group comparison, reflecting marked task difference in the saccade rate in the control group and, on the other hand, almost equal numbers of reflexive saccades made in the Instructed and Non-instructed tasks by the patients with mediofrontal lesions.

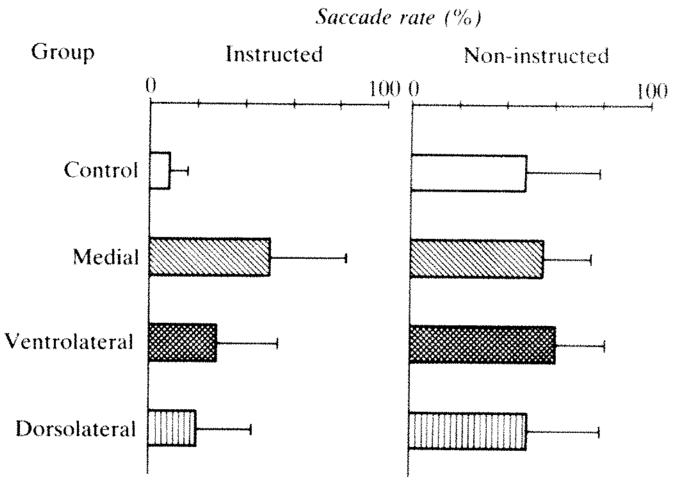

FIG. 2. Overall saccade rate for each group of subjects in the Instructed and the Non-instructed tasks.

TABLE 2. TWO-WAY ANOVA OF THE SACCADE RATE

	Main Effect				*Interaction (Group × Task)*	
	Group		*Task*			
	F	*P*	*F*	*P*	*F*	*P*
All groups combined	4.5	0.007	31.7	0.0001	3.2	0.03
Control vs dorsolateral	0.7	0.4	43.1	0.0001	1.1	0.3
Control vs ventrolateral	8.3	0.007	55.3	0.0001	0.4	0.5
Control vs medial	16.1	0.001	6.5	0.02	7.8	0.01

Direction specific saccade rate. The direction of reflexive saccades in relation to the side of the lesion (contralateral or ipsilateral) was analysed. In the control subjects, the rate of left- and rightward saccades was compared. Fig. 3 shows the rate of contralateral and ipsilateral or leftward and rightward saccades in patients and controls, respectively.

A three-way ANOVA was performed on saccade rate for the patients. This analysis yielded no significant main effect of group [F(2,30) = 1.5, n.s.], but a significant effect of task [F(1,30) = 15.5, $P < 0.001$] and saccade direction [F(1,30) = 24.8, $P < 0.0001$]. Saccade direction interacted significantly with group [F(2,30) = 5.5, $P < 0.01$], as well as with task [F(1,30) = 5.7, $P < 0.05$]. A significant interaction between all the factors analysed was found [F(2,30) = 3.99, $P < 0.05$]. In the medial group, an *a posteriori* comparison revealed a highly significant ($P < 0.001$) difference between contra- and ipsilaterally directed saccades in the Instructed task. In the ventrolateral group, this comparison yielded a significant ($P < 0.05$) difference between the rate of contra- and ipsilaterally directed saccades in the Non-instructed task. However, further analysis revealed that these saccade-rate asymmetries are associated, in both groups

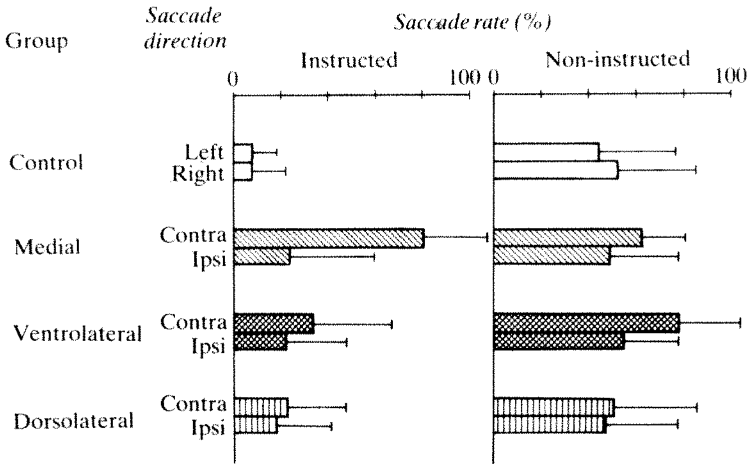

FIG. 3. Direction-specific saccade rate for each group of subjects in both the Instructed and the Non-instructed tasks.

of patients, mainly with left-hemisphere lesions (*see* Side-of-lesion section *below*). In the dorsolateral group, no asymmetry in the saccade rate was found either in the Instructed or in the Non-instructed tasks.

Fig. 4 shows the direction-specific saccade rate of a total of 7 patients with frontomedial lesions. The empty bars indicate trials with contralateral peripheral stimuli. The hatched bars represent trials with ipsilateral stimuli. The cortical lesions, as demonstrated by CT scans, are shown in black on a schematic brain diagram along the bar graph.

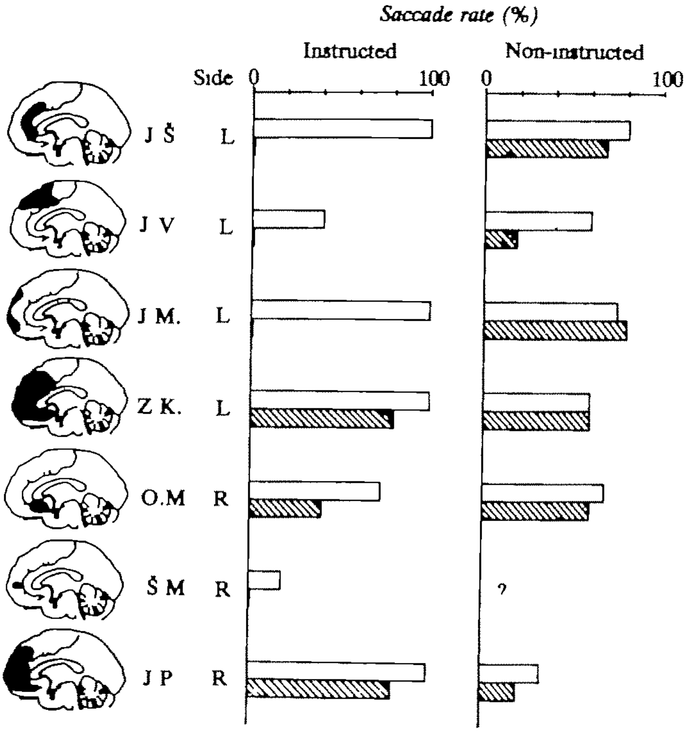

Fig. 4. Individual data for the patients in the medial group. The CT-based extent of cortical lesion for each patient is shown on a medial view of the right hemisphere next to the initials identifying the patients. L/R signify the side of the lesion. The empty bars indicate trials in which peripheral stimuli were presented in the contralateral hemifield. The hatched bars represent trials with ipsilateral stimuli. '?' indicates that in patient S.M., the Non-instructed task was not completed.

The most asymmetrical deficit was associated with an anterior cingulate gyrus lesion (J.S.), a supplementary motor area lesion (J.V.) and combination of ventrolateral and medial lesion (J.M.). The lesion was in the left hemisphere in all of these patients. A bidirectional deficit (accentuated contralaterally) was found in 2 patients (Z.K. and J.P.) who had a large medial lesion extending through the supplementary motor area and the anterior cingulate gyrus. In Z.K., the only patient with bilateral medial frontal lobe lesions, the left-sided damage was greater and, for the purpose of statistical analysis, the rightward saccades were considered to be the contralateral ones. In the Non-instructed task, a symmetrical distribution of saccades in all but one (J.V.) fronto-medial patient was found. One patient (S.M.) did not complete the Non-instructed task because of a technical failure.

Two-way ANOVA was performed on saccade rate for the controls. This analysis yielded significant main effect of task [$F(1,18) = 30.7$, $P < 0.001$] only. The main effect of saccade direction [$F(1,18) = 1.3$, n.s.], as well as task×direction interaction [$F(1,18) = 1.3$, n.s.] did not reach significance.

Saccade latency and peripheral stimulus fixation time. Mean latencies of reflexive saccades and fixation time are summarized in Table 3. The saccade latency and fixation time were analysed as a 4 (group)×2 (task) factorial analysis of variance. This analysis did not yield any significant main effect of saccade latency. There were no significant interactions.

TABLE 3. LATENCIES OF REFLEXIVE SACCADES (A) AND TIME OF GAZE FIXATION ON THE PERIPHERAL STIMULUS (B) OBTAINED IN THE INSTRUCTED AND THE NON-INSTRUCTED TASKS (MEAN ±SD)

	Group			
Task	*Dorsolateral*	*Ventrolateral*	*Medial*	*Control*
A. Latencies (Mean ± SD) of the reflexive saccades				
Instructed	231 ± 76	281 ± 116	240 ± 115	287 ± 125
Non-instructed	281 ± 84	283 ± 96	270 ± 91	293 ± 91
B. Time of peripheral stimulus fixation (Mean ± SD)				
Instructed	222 ± 57	282 ± 170	293 ± 168	217 ± 63
Non-instructed	218 ± 71	202 ± 51	249 ± 101	195 ± 56

The same analysis carried out on the fixation time yielded a marginally significant main effect of task [$F(1,34) = 3.1$, $P = 0.08$]. No significant interaction was again found. Paired comparison of fixation time (control vs each one of the patient groups) performed by a two-way ANOVA revealed a significant main effect of group in the control vs medial group comparison [$F(1,40) = 4.9$, $P < 0.05$; fixation time was longer in both tasks in the medial group] and a significant task effect in the control vs ventrolateral group comparison [$F(1,58) = 4.2$, $P < 0.05$; fixation time was longer in the Instructed task in both groups] only.

Saccade direction factor has not been analysed here as there was a small number of cases available for analysis.

Verbal report. Peripheral stimuli were noted by 100% of the control subjects and 94% of the patients (the medial, the ventrolateral and the dorsolateral groups altogether) in the Instructed task. In the Non-instructed task, the perception of peripheral stimuli was reported by 90% of the controls, but only 61% of the patients. Using the Exact Fisher test for four-fold table, a significant effect of group was obtained in this task ($P = 0.03$). In the Instructed task, 37% of the controls and 33% of the patients reported eye movements toward the peripheral stimuli. In the Non-instructed task, there was 16% of the controls and 27% of the patients reporting these eye movements. The Fisher test did not yield a significant effect of task in any group.

Thus, there was a marked discrepancy between the subject's report of eye movements and the occurrence of reflexive saccades as verified by EOG (*see* Fig. 5).

WCST and WF

The results of WCST and WF are summarized in Table 4. One-way ANOVA with group as a main factor yielded a significant effect of this factor upon all of the WCST parameters and on the number of words produced within the first 30 s of the test. No significant group effect on the number of words produced in the second 30 s of the WF test was found. *A posteriori* comparison revealed significant differences between the control and medial groups in all but the relative number of perseverative errors and the rate of unique responses ($P < 0.05$). A significant ($P < 0.05$) group difference was found in all WCST parameters in the control vs ventrolateral group comparison. Finally, in the control vs dorsolateral group comparison, the only significant group

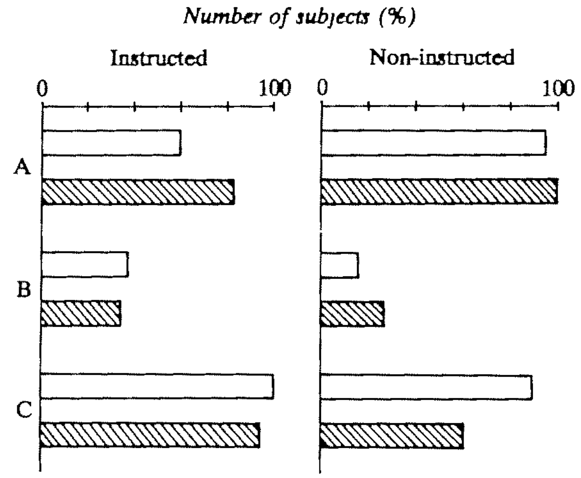

FIG 5 Percentage of subjects making one or more reflexive saccades (A), noticing the appearance of the peripheral stimulus (B), and reporting eye movements toward these stimuli (C). The empty and hatched bars represent control subjects and patients, respectively.

TABLE 4 PERFORMANCE OF THE SUBJECTS ON THE MODIFIED WISCONSIN CARD SORTING AND THE WORD FLUENCY TESTS (MEAN ±SD)

	Group			
Task	*Dorsolateral*	*Ventrolateral*	*Medial*	*Control*
WCST−TE	14.1±10.1	16.7±11.0	18 0± 9.8	8 3± 8 3
WCST−Cat	4.9± 1.9	4.3± 1.9	4.0± 2 0	5.9± 1 5
WCST−PE%	36 0±17 4	33 8±15.3	21.8±16.3	20.6±16.8
WCST−U	1.1± 1.9	1.8± 3.2	1.8± 3.1	0.1± 0.3
WF (0 to 30 s)	8.7± 1 0	7.9± 2.3	7.3± 2.5	9.9± 2.3
WF (31 to 60 s)	5.3± 1 0	4.1± 1.5	4.3± 2.8	5 3± 1.8

difference was revealed in the relative number of PE. The same comparison revealed a significantly lower number of words produced in the first 30 s of the WF test in the medial ($P < 0.05$) and ventrolateral ($P < 0.01$) groups.

Inter-task correlations

Correlation coefficients were computed among the main parameters of the task administered in the ventrolateral and the control groups only.

Significant correlations were found between the saccade rate and the fixation time in the Instructed task in the ventrolateral ($r = 0.62$, $P < 0.01$) as well as in the control ($r = 0.52$, $P < 0.05$) groups. In the Non-instructed task, this relationship was significant in the control group only ($r = 0.56$, $P < 0.05$). The longer the fixation time in one task, the higher the saccade rate in the same one. In the ventrolateral group, saccade rate in the Non-instructed task was correlated with the latency of saccades performed in the same task: $r = -0.66$ ($P < 0.01$). The shorter the saccade latency, the higher saccade rate in this task. This correlation could not be demonstrated in the control group.

Significant correlations were not found between any of the oculomotor task parameters and neither the WCST nor the WF parameters. The only exception from this negative finding was a significant correlation between the fixation time in the Instructed task and the number of unique responses in the WCST ($r = 0.73$, $P < 0.01$) in the ventrolateral group.

Side-of-lesion effect

A side-of-lesion analysis in all parameters was limited to the ventrolateral group because an adequate number of subjects with left- ($n = 9$) and right- ($n = 9$) sided lesions was available only in this group. However, as the difference between contra- and ipsilaterally directed saccades seemed to be of great importance, we have decided to analyse this parameter in all patient groups keeping in mind the limitation due to the low number of subjects within the left/right dorsolateral and especially the left/right medial groups.

The difference between the rate of contralaterally minus ipsilaterally directed saccades (contra-minus-ipsi difference) has been analysed by means of three-way ANOVA with group (medial, ventrolateral and dorsolateral), side of the lesion (left and right) and task (Instructed and Non-instructed) as main factors. This analysis yielded a significant main effect of group [$F(1,28) = 3.9$, $P < 0.05$] and side of lesion [$F(1,28) = 7.5$, $P < 0.01$] but not of task [$F(1,28) = 2.8$, $P = 0.1$]. The only (marginally significant) interaction was that between all factors: group×side×task interaction [$F(2,28) = 2.7$, $P = 0.08$]. An *a posteriori* comparison (*see* Fig. 6) yielded a significant difference between the rate of contra- and ipsilaterally directed saccades only for the left-medial group in the Instructed task ($P < 0.001$) and for the left-ventrolateral group in the Non-instructed one ($P < 0.005$). Furthermore, the same analysis revealed significant *task* difference in the contra-minus-ipsi difference in the left-medial ($P < 0.01$) but not in the left-ventrolateral groups. Nevertheless, it should be stressed here that the task difference goes in the opposite direction in these groups (in the left-medial group, contra-minus-ipsi difference being greater in the Instructed task, whereas in the left-ventrolateral group this parameter was of greater value in the Non-instructed task). The contra-minus-ipsi difference did not differ significantly from zero either in the right-medial or in the right-ventrolateral or the right- or left-dorsolateral groups.

In the ventrolateral group only, an *a posteriori* comparison was also carried out between the patients with left-sided lesions and those with right-sided ones on the overall saccade rate in the Instructed and the Non-instructed tasks, as well as the various parameters of the WCST and the WF test. No significant differences were found in any of those comparisons.

DISCUSSION

The present study demonstrated that the effect of unilateral lesions of the frontal lobe on the stability of central-gaze fixation depends both on the *mode* of gaze-fixation maintenance (voluntary vs automatic) and the *site* of the lesion (dorsolateral, ventrolateral, or medial). Furthermore, our data suggest that *side* of lesion (left vs right hemisphere) might also be of importance.

In the Non-instructed task, in which central-gaze fixation was maintained by an automatic foveation mechanism, no significant group differences were found in total saccade rate. Thus, reactivity to suddenly appearing peripheral stimuli was equal in all of the groups. The only exception to this rule was the group of patients with ventrolateral lesions in the left frontal lobe (*see below*).

In the Instructed task, no significant impairment in maintaining verbally instructed central-gaze fixation was found in the *dorsolateral* group. The lesions were located at the posterior part of the middle frontal gyrus in all of the patients constituting this group. In some of them, the lesion extended to the upper parts of the precentral (2 patients) or the superior frontal gyri (2 patients). In another 2 patients the lesion was more extensive, encroaching upon the anterior part of the medial frontal gyrus (i.e. the area affected in most of the patients in the ventrolateral group). In one of these patients, we observed the highest rate of reflexive saccades in the Instructed task by the patients from within the dorsolateral group. In the dorsolateral group, the lesions probably involved the Frontal Eye Fields (FEF) as is suggested by a comparison between the location of the lesions in these patients and the known FEF site (Penfield and Boldrey, 1937; Penfield and Rasmussen, 1950; Penfield and Jasper, 1954). The FEF are classically thought to be involved in some aspects of oculomotor control (*see*, e.g. Goldberg and Segraves, 1990). However, in non-human primates, lesion studies failed to demonstrate any long-term deficit in visually guided and/or spontaneous saccades following unilateral FEF lesions (Latto and Cowey, 1971*a,b*; Schiller *et al.*, 1980; Rizzolatti *et al.*, 1983). The only long-term deficit associated with unilateral lesions of the FEF has been demonstrated in learning and performing memory-guided saccades to the contralateral hemifield (Deng *et al.*, 1986). In man, Guitton *et al.* have shown in 5 patients a strong bilateral deficit in suppressing reflexive glances (during an anti-saccade task) following a unilateral lesion to the dorso-medial frontal cortex (Guitton *et al.*, 1985). This deficit cannot be linked, however, exclusively to the FEF as the lesions of all of these patients '... extended into the mesial side of the hemisphere and almost certainly encroached on the frontal supplementary motor area' (Guitton *et al.*, 1985, p. 467). Thus, it might be concluded that neither our nor Guitton's studies provide enough evidence for an exclusive role of the FEF in the higher-order control of saccadic eye movements.

In the *medial* group, severe deficit in voluntary suppression of reflexive saccades was found. This deficit was unidirectional to a different degree in all of the medio-frontal patients (*see* Fig. 4). In 2 patients (J.M., J.S.) a clearly unidirectional deficit was observed: these patients made 100% of their reflexive saccades to the stimuli presented within the contralateral hemifield and they suppressed all saccades triggered from the ipsilateral hemifield. The lesions encroached upon the left anterior cingulate gyrus in one of these patients (J.S.) and the ventrolateral as well as the medial parts of the left pre-frontal cortex in the other one (J.M.). In another patient (J.V.), the left supplementary motor area (SMA) was perhaps damaged. Finally, the strongest deficit (also in the voluntary suppression of ipsilaterally directed saccades) was found in patients with lesions extending throughout the medial wall affecting thus both the SMA and anterior cingulate gyrus (within the left hemisphere in Z.K., and in the right hemisphere in J.P.). The asymmetry of Instructed-task deficit was significant only in patients with left-sided lesions (Fig. 6). This fact cannot be interpreted simply by differences in size and/or site of the lesions between the left and right subgroups of the medio-frontal patients as the total saccade rate did not significantly differ between these subgroups. However, due to the low number of patients in the medial group the above-mentioned left vs right difference should be viewed only as a preliminary finding.

Previous studies have shown that the medio-frontal structures [the SMA and anterior cingulate cortex constituting a reciprocally interconnected system (Damasio and Van Hoesen, 1980)] are involved in the control of complex motor behaviour (e.g. Talairach *et al.*, 1973; Laplane *et al.*, 1977; Goldberg, 1985), as well as in the regulation of eye movements (Melamed and Larsen, 1979; Fox *et al.*, 1985). The presence of the 'alien hand sign' (Shahani *et al.*, 1970; Goldberg *et al.*, 1981; Mori and Yamadori, 1982; Stuss and Benson, 1986, p. 87) in patients with acute lesions of the medial wall of the frontal lobe seems to be especially relevant in regard to the interpretation of our data. The 'alien hand sign' is characterized by (1) forced grasping, (2) motor perseveration and (3) presence of externally triggered automatic purposeful movements dissociated

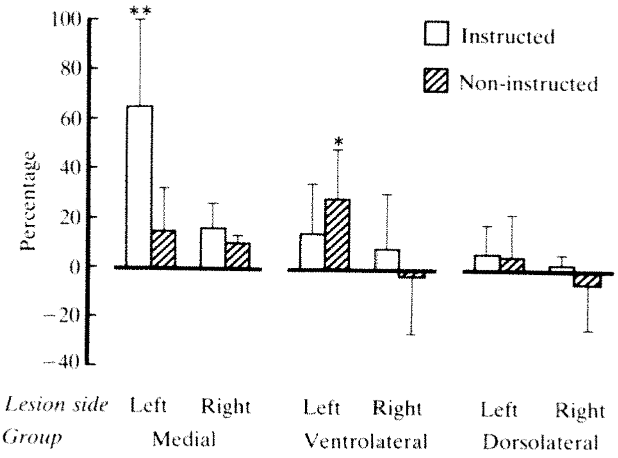

FIG. 6. Difference in the percentage of saccades made towards the peripheral stimuli presented within the contralateral and the ipsilateral hemifields. The empty and hatched bars represent contra-minus-ipsi difference in the Instructed and the Non-instructed tasks, respectively. The asterisks indicate the significance of the contra-minus-ispsi difference from zero. $*P < 0.005$; $**P < 0.001$.

from conscious volition—with all of these signs limited to the arm contralateral to the lesion (Goldberg *et al.*, 1981). The inability to suppress voluntarily reflexive saccades triggered from within a contralateral hemifield might be viewed as a chronic oculomotor variant of the acute and transient alien hand sign. Furthermore, the alien hand sign seems to occur more frequently in cases with *left*-sided lesions, an observation which is in accordance with our finding of the significant asymmetry in voluntary suppression of externally triggered saccades following the lesions to the left medio-frontal lobe.

Similar aspects of the (oculo) motor control might also take place at other levels of the motor system. This fact is probably reflected in our observation of the unidirectional type of deficit in voluntary suppression of reflexive saccades obtained in 3 patients with unilateral lesions to the *basal ganglia* (Fig. 7). In these patients, the head of caudate nucleus (M.B.), the head and body of caudate nucleus and part of external capsule (M.K.) and the body of caudate nucleus and external capsule (M.Bo.) were damaged on the right, left and right side, respectively. Lesions restricted within the external capsule were not found to result in such a deficit in 2 other patients examined (not shown). The medial frontal structures are closely related to the basal ganglia. Neurons within the medial frontal cortex project to the striatum (Leichnetz and Astruc, 1976; Yeterian and Van Hoesen, 1978; Baleydier and Mauguiere, 1980; Damasio and Van Hoesen, 1980; Fotuhi *et al.*, 1990; Lee and Deutch, 1990). The contribution of the substantia nigra (Wurtz and Hikosaka, 1986) and caudate nucleus (Miyashita *et al.*, 1990; Usui *et al.*, 1990) to the control of spontaneous, visually guided and, most important, memory-guided saccadic eye movements has been shown in monkeys using a chemical-lesion technique. In man, a severe impairment in suppressing reflexive saccades has been shown in patients with Huntington's disease (Lasker *et al.*, 1987), but not in patients with

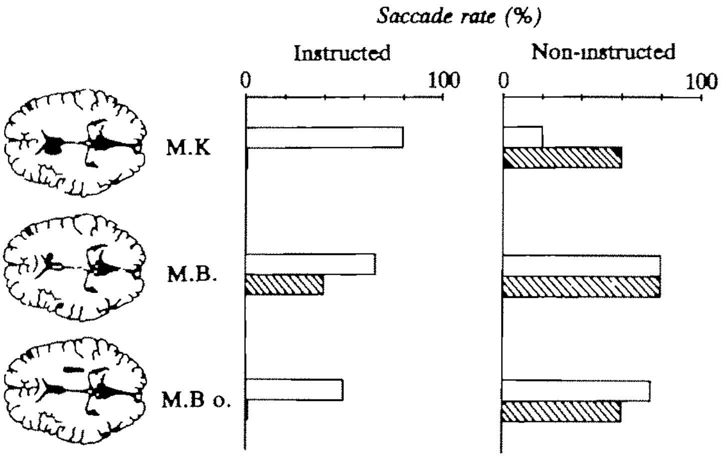

FIG. 7 Individual data of the patients with lesions of the caudate nucleus. The CT-based extent of cortical lesion from each patient is shown on the horizontal section of the brain next to the initials identifying the patients The empty bars indicate trials in which peripheral stimuli were presented in the contralateral hemifield. The hatched bars represent trials with ipsilateral stimuli.

Parkinson's disease (Lueck *et al.*, 1990). In the later study, however, a deficit in memory-guided saccades was demonstrated (Lueck *et al.*, 1990). A severe deficit in suppressing reflexive saccades has also been found in patients with progressive supranuclear palsy (Pierrot-Deseilligny *et al.*, 1989) where different subcortical and fronto-cortical neural structures are thought to be involved.

The Instructed-task data in the medial group together with the case studies of patients with the alien hand sign suggest that the medial frontal structures are involved in voluntary (i.e. internally) guided suppression of interfering motor programs that are triggered from within the contralateral hemispace. The contributions of the SMA and the cingulate cortex to different aspects of this control mechanism are not clear. Furthermore, the basal ganglia are probably involved in this higher-order regulation as well.

In the *Ventrolateral* group, a significant deficit in voluntary suppression of reflexive saccades was found. This deficit was bidirectional with a slight but non-significant tendency to make more contralaterally directed saccades. Subsequent analysis of the left- vs right-sided lesions did not reveal, however, any significant difference between contra- and ipsilaterally directed saccades (Fig. 7) unlike that observed in the medial group. The contra-minus-ipsi asymmetry in the saccade rate, however, proved to be significant in the Non-instructed task. Patients with left-sided lesions made more reflexive saccades to the right than to the left, whereas the number of saccades triggered from the left and right hemifield was equal in patients with right-sided ventrolateral lesions. Thus, it might be suggested that the reactivity of patients with the left-sided ventrolateral lesions to the stimuli presented within their contralateral (that is right) visual hemifield is higher than normal. A similar type of asymmetry in reactivity to extraneous stimuli following lesions to the frontal lobe has been reported in the study by Knight *et al.* (1980). In this study, higher reactivity to auditory stimuli (reflected in enhancement of *N*1 amplitudes of evoked potentials to contralaterally presented tone stimuli) was observed following both left- and right-sided lesions to the frontal lobe and was greater for patients with right-hemisphere damage. Despite the reversed effect of the side of the lesion, both our and Knight's findings are consistent with the idea that the frontal cortex might be involved in the control of gating of thalamic input to the cerebral cortex (Skinner and Yingling, 1977).

A functional interpretation of the bidirectional deficit observed in the ventrolateral group in the Instructed task is not straightforward. First of all, it should be pointed out that lesions in this group had affected not only the cortex itself but also adjacent white matter and thus could have interrupted (in some patients) some of the connections between the medial frontal structures and the other brain regions (e.g. basal ganglia). Second, this area of the frontal cortex is thought to be involved in different functions which might be related to the performance on the Instructed task. In subhuman primates, lesions to the principal sulcus (the area of the lateral frontal cortex roughly corresponding to the anterior portion of the medial frontal gyrus in man) have been shown to induce a deficit in manual (e.g. Fuster and Alexander, 1970), as well as oculomotor (Funahashi *et al.*, 1986) delayed tasks (*see* Goldman-Rakic, 1987, for review). A similar type of deficit has been shown following the mid-lateral frontal lesions in the task requiring not only an active maintaining of external cues but also (more important) monitoring the self-generated responses (Petrides, 1989). Another type of deficit, a difficulty in learning to withhold responses to the negative stimulus in go/no-go tasks, has been demonstrated following more ventrally located lesions of the monkey prefrontal cortex (Iversen and Mishkin, 1970). The involvement of the lateral frontal cortex in go/no-go performance has also obtained support from electrophysiological studies (Sasaki and Gemba, 1986; Watanabe, 1986; Sasaki *et al.*, 1989). In patients with lesions within the lateral frontal cortex, a pattern of neuropsychological deficit is less clear. An impairment in delayed tasks is difficult to obtain probably due to the possible use of verbal mediation (Milner, 1964; Freedman and Oscar-Berman, 1986). A go/no-go deficit has been found in patients with frontal (vs temporal) (Toczek, 1960; Drewe, 1975) and medio-frontal (Leimkuhler and Mesulam, 1985; Verfaellie and Heilman, 1987) lesions. Deficits in subject-ordered tasks have been demonstrated, especially following left frontal lesions (Petrides and Milner, 1982). The classical neuropsychological impairment associated with lateral frontal lesions is that picked up in Wisconsin Card Sorting Test (Milner, 1964, 1982; Milner and Petrides, 1984). This deficit may be interpreted as the result of the patient's inability to suppress a strong, competing response tendency (Mishkin, 1964). Thus, the bilateral deficit in suppressing voluntarily reflexive saccades we observed in our ventrolateral group on the Instructed task might be attributed to either their inability to maintain actively (hold 'on-line') a verbally instructed program of behaviour or to an impairment in suppressing the inappropriate alternatives interfering with that program or both.

In conclusion, our data have provided further support for the idea of functional heterogeneity of the frontal cortex. Lesions to different regions of the frontal lobe (i.e. medial vs ventrolateral) yielded different patterns of deficit in voluntary suppression of reflexive saccades. Furthermore, the non-specific effect of frontal lesions on general reactivity (or disinhibition) could be ruled out in all of these groups.

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REFERENCES

Baleydier C, Mauguiere F (1980) The duality of the cingulate gyrus in monkey. neuroanatomical study and functional hypothesis. *Brain*, **103**, 525–554.

Bianchi L (1922) *The Mechanism of the Brain and the Function of the Frontal Lobes*. New York: William Wood and Edinburgh: E. and S. Livingstone.

Chapman LJ, Chapman JP (1987) The measurement of handedness. *Brain and Cognition*, **6**, 175–183.

Damasio AR, Van Hoesen GW (1980) Structure and function of the supplementary motor area. *Neurology, New York*, **30**, 359.

Deng S-Y, Goldberg ME, Segraves MA, Ungerleider LG, Mishkin M (1986) The effect of unilateral ablation of the frontal eye fields on saccadic performance in the monkey. In: *Adaptive Processes in Visual and Oculomotor Systems*. Edited by E. L. Keller and D. S. Zee. Oxford: Pergamon Press, pp. 201–208.

DREWE EA (1975) Go-no go learning after frontal lobe lesions in humans. *Cortex*, **11**, 8–16.

FOLSTEIN MF, FOLSTEIN SE, MCHUGH PR (1975) 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

FOTUHI M, KOLIATSOS VE, ALEXANDER GE, DELONG MR (1990) Differential organization of inputs to neostriatum from paired pre- and post-central cortical areas. *Society for Neuroscience Abstracts*, **16**, 1230.

FOX PT, FOX JM, RAICHLE ME, BURDE RM (1985) The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomographic study. *Journal of Neurophysiology*, **54**, 348–369.

FREEDMAN M, OSCAR-BERMAN M (1986) Bilateral frontal lobe disease and selective delayed response deficits in humans. *Behavioral Neuroscience*, **100**, 337–342.

FUNAHASHI S, BRUCE CJ, GOLDMAN-RAKIC PS (1986) Perimetry of spatial memory representation in primate prefrontal cortex: evidence for a mnemonic hemianopia. *Society for Neuroscience Abstracts*, **12**, 554.

FUSTER JM, ALEXANDER GE (1970) Delayed response deficit by cryogenic depression of frontal cortex *Brain Research, Amsterdam*, **20**, 85–90.

GOLDBERG G (1985) Supplementary motor area structure and function: review and hypotheses. *Behavioral and Brain Sciences*, **8**, 567–615.

GOLDBERG G, MAYER NH, TOGLIA JU (1981) Medial frontal cortex infarction and the alien hand sign. *Archives of Neurology, Chicago*, **38**, 683–686.

GOLDBERG ME, SEGRAVES MA (1990) The role of the frontal eye field and its corticotectal projection in the generation of eye movements. *Research Publications: Association for Research in Nervous and Mental Disease*, **67**, 195–209.

GOLDMAN-RAKIC PS (1987) Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: *Handbook of Physiology*, Section I, Volume 5, Part 1. Edited by V. B Mountcastle. Bethesda, MD: American Physiological Society, pp. 373–417.

GUITTON D, BUCHTEL HA, DOUGLAS RM (1985) Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades *Experimental Brain Research*, **58**, 455–472.

IVERSEN SD, MISHKIN M (1970) Perseverative interference in monkeys following selective lesions of the inferior prefrontal convexity. *Experimental Brain Research*, **11**, 376–386.

KNIGHT RT, HILLYARD SA, WOODS DL, NEVILLE JH (1980) The effects of frontal and temporal-parietal lesions on the auditory evoked potential in man. *Electroencephalography and Clinical Neurophysiology*, **50**, 112–124.

LAPLANE D, TALAIRACH J, MEININGER V, BANCAUD J, ORGOGOZO JM (1977) Clinical consequences of corticectomies involving the supplementary motor area in man. *Journal of Neurological Sciences*, **34**, 301–314.

LASKER AG, ZEE DS, HAIN TC, FOLSTEIN SE, SINGER HS (1987) Saccades in Huntington's disease: initiation defects and distractibility. *Neurology, Cleveland*, **37**, 364–370.

LATTO R, COWEY A (1971*a*) Visual field defects after frontal eye-field lesions in monkeys. *Brain Research, Amsterdam*, **30**, 1–24.

LATTO R, COWEY A (1971*b*) Fixation changes after frontal eye-field lesions in monkeys. *Brain Research, Amsterdam*, **30**, 25–36

LEE MC, DEUTCH AY (1990) Organization of medial prefrontal cortical projections to the ventral striatum. *Society for Neuroscience Abstracts*, **16**, 1230.

LEICHNETZ GR, ASTRUC J (1976) The efferent projections of the medial prefrontal cortex in the squirrel monkey (*Saimiri sciureus*). *Brain Research, Amsterdam*, **109**, 455–472.

LEIMKUHLER ME, MESULAM M-M (1985) Reversible go–no go deficits in a case of frontal lobe tumor. *Annals of Neurology*, **18**, 617–619.

LUECK CJ, TANYERI S, CRAWFORD TJ, HENDERSON L, KENNARD C (1990) Antisaccades and remembered saccades in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **53**, 284–288.

LURIA AR (1980) *Higher Cortical Functions in Man.* Second edition. New York: Basic Books.

MELAMED E, LARSEN B (1979) Cortical activation pattern during saccadic eye movements in humans: localization by focal cerebral blood flow increases. *Annals of Neurology*, **5**, 79–88.

MILNER B (1964) Some effects of frontal lobectomy in man. In: *The Frontal Granular Cortex and Behavior.* Edited by J. M. Warren and K. Akert. New York and London: McGraw-Hill, pp. 313–334.

MILNER B (1982) Some cognitive effects of frontal-lobe lesions in man. *Philosophical Transactions of the Royal Society of London, B*, **298**, 211–226.

MILNER B, PETRIDES M (1984) Behavioural effects of frontal-lobe lesions in man. *Trends in Neurosciences*, 7, 403–407.

MISHKIN M (1964) Perseveration of central sets after frontal lesions in monkeys. In: *The Frontal Granular Cortex and Behavior*. Edited by J. M. Warren and K. Akert. New York and London: McGraw-Hill, pp. 219–241.

MIYASHITA N, MATSUMURA M, USUI S, KATO M, KORI A, GARDINER TW *et al.* (1990) Deficits in task-related eye movements induced by unilateral infusion of MPTP in the monkey caudate nucleus. *Society for Neuroscience Abstracts*, **16**, 235.

MORI E, YAMADORI A (1982) Compulsive manipulation of tools and pathological grasp phenomenon. *Clinical Neurology, Tokyo*, **22**, 329–335 (in Japanese).

NELSON HE (1976) A modified card sorting test sensitive to frontal lobe defects. *Cortex*, **12**, 313–324.

PENFIELD W, BOLDREY E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, **60**, 389–443.

PENFIELD W, RASMUSSEN T (1950) *The Cerebral Cortex of Man: A Clinical Study of Localization of Function*. New York. Macmillan.

PENFIELD W, JASPER HH (1954) *Epilepsy and the Functional Anatomy of the Human Brain*. Boston: Little, Brown.

PETRIDES M (1989) Frontal lobes and memory. In: *Handbook of Neuropsychology*, Volume 3. Edited by F. Boller and J. Grafman. Amsterdam: Elsevier, pp. 75–90.

PETRIDES M, MILNER B (1982) Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man *Neuropsychologia*, **20**, 249–262.

PIERROT-DESEILLIGNY C, RIVAUD S, PILLON B, FOURNIER E, AGID Y (1989) Lateral visually-guided saccades in progressive supranuclear palsy. *Brain*, **112**, 471–487.

RIZZOLATTI G, MATELLI M, PAVESI G (1983) Deficits in attention and movement following the removal of postarcuate (area 6) and prearcuate (area 8) cortex in macaque monkeys. *Brain*, **106**, 655–673.

SASAKI K, GEMBA H (1986) Electrical activity in the prefrontal cortex specific to no-go reaction of conditioned hand movement with colour discrimination in the monkey. *Experimental Brain Research*, **64**, 603–606.

SASAKI K, GEMBA H, TSUJIMOTO T (1989) Suppression of visually initiated hand movement by stimulation of the prefrontal cortex in the monkey. *Brain Research, Amsterdam*, **495**, 100–107.

SCHILLER PH, TRUE SD, CONWAY JL (1980) Deficits in eye movements following frontal eye-field and superior colliculus ablations. *Journal of Neurophysiology*, **44**, 1175–1189.

SHAHANI B, BURROWS P, WHITTY CWM (1970) The grasp reflex and perseveration. *Brain*, **93**, 181–192.

SHALLICE T (1982) Specific impairments of planning. *Philosophical Transactions of the Royal Society of London, B*, **298**, 199–209.

SKINNER JE, YINGLING CD (1977) Central gating mechanisms that regulate event-related potentials and behavior: a neural model for attention. In: *Attention, Voluntary Contraction and Event-Related Cerebral Potentials. Progress in Clinical Neurophysiology*, Volume 1. Edited by J. E. Desmedt. Basel: S. Karger, pp. 30–69.

STUSS DT, BENSON DF (1986) *The Frontal Lobes*. New York: Raven Press.

TALAIRACH J, BANCAUD J, GEIER S, BORDAS-FERRER M, BONIS A, SZIKLA G *et al.* (1973) The cingulate gyrus and human behaviour. *Electroencephalography and Clinical Neurophysiology*, **34**, 45–52.

TOCZEK S (1960) Disturbances of inhibitory processes due to lesions in the frontal area of the brain in man. *Acta Biologiae Experimentalis*, **20**, 103–114.

USUI S, KATO M, KORI A, MATSUMURA M, MIYASHITA N, HIKOSAKA O (1990) Deficits in spontaneous eye movements induced by unilateral infusion of MPTP in the monkey caudate nucleus. *Society for Neuroscience Abstracts*, **16**, 235.

VERFAELLIE M, HEILMAN KM (1987) Response preparation and response inhibition after lesions of the medial frontal lobe. *Archives of Neurology, Chicago*, **44**, 1265–1271.

WATANABE M (1986) Prefrontal unit activity during delayed conditional Go/No-go discrimination in the monkey. II. Relation to Go and No-go responses. *Brain Research, Amsterdam*, **382**, 15–27.

WURTZ RH HIKOSAKA O (1986) Role of the basal ganglia in the initiation of saccadic eye movements. *Progress in Brain Research*, **64**, 175–190.

YETERIAN EH, VAN HOESEN GW (1978) Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. *Brain Research, Amsterdam*, **139**, 43–63.

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A CASE OF OCULAR TILT REACTION AND TORSIONAL NYSTAGMUS DUE TO DIRECT STIMULATION OF THE MIDBRAIN IN MAN

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SUMMARY

A case is presented of a patient who underwent insertion of a periaqueductal grey electrode for the relief of chronic pain. Shortly after insertion, the patient developed a left-sided ocular tilt reaction (OTR). The electrode tip, initially to the right of the midline, was then withdrawn slightly so that it was now on the left side. Stimulation at this point gave rise to a worsening of the tilt reaction, in addition to bilateral counter-clockwise torsional nystagmus. Computerized tomography and stereotactic coordinates indicated that the tip of the electrode was finally situated in the region of the left interstitial nucleus of Cajal (INC). The production of an OTR by stimulation in this region is similar to the phenomenon previously reported in monkeys and cats The side of the OTR is consistent with previous evidence, suggesting that the utricular pathways cross between medulla and midbrain

INTRODUCTION

The ocular tilt reaction (OTR) is a particular variety of skew deviation, comprising the triad of vertical separation of the eyes (hypertropia), ocular cyclorotation and head tilt. It is thought to be mediated through the otolithic (especially utricular) pathways, and was first described in detail in the monkey by Westheimer and Blair (1975*a,b*) as the result of stimulation in the region of the interstitial nucleus of Cajal (INC), located in the midbrain. While skew deviation has little localizing value as a clinical sign, even with regard to the side of the lesion (Goldstein and Cogan, 1961; Smith *et al.*, 1964; Garelli and Gherardini, 1972; Keane, 1975, 1985), the OTR has been shown to be more specific (Halmagyi *et al.*, 1990).

Several clinical reports of eye movements in response to brainstem electrical stimulation have been reported by Nashold and co-workers (Nashold and Gills, 1967; Nashold, 1970; Nashold and Seaber, 1972; Seaber and Nashold, 1980) and others (Spiegel *et al.*, 1964; Sano *et al.*, 1972). Torsional movements were not reported in these studies. The present report is of a man in whom periaqueductal grey stimulation was attempted for the relief of chronic pain. An initial lesion following electrode placement in the midbrain produced a contralateral OTR, while subsequent electrical stimulation after withdrawal of the electrode across the midline produced an ipsilateral one, in addition to torsional nystagmus. Clinical evidence supporting crossed utricular pathways is thus provided.

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This case also represents the first report of torsional eye movements resulting from direct electrical stimulation of the midbrain in man.

CASE HISTORY

V.L., a 47-yr-old Caucasian male, was admitted for insertion of an electrode in the periaqueductal grey matter for the relief of neuralgic pain in June 1988. Twenty-eight years previously, he had suffered a road traffic accident which resulted in intradural tears of the lower cervical and first thoracic nerve roots on the right. This left him with an almost paralysed right arm which was almost totally anaesthetic below the elbow and which exhibited altered sensation between the shoulder and the elbow. Three weeks after the accident he developed neuralgic pain in the right hand and forearm, and this had gradually worsened ever since. He had previously tried various therapies, none of which were helpful.

On examination, his right arm was wasted and flaccid, apart from some residual movement in the biceps muscle. The right arm was areflexic and showed anaesthesia to all sensory modalities below the elbow, except for a strip along the radial border of the forearm. The remainder of the examination was normal.

He underwent the first stage of the stereotaxic operation under general anaesthesia at which a Watkins sphere (Watkins, 1974) was positioned on the basis of the foramen of Monro–posterior commissure (FM–PC) line coordinates as derived from a ventriculogram using a Bennett frame (Bennett, 1960). Three days later the actual positioning of the stimulating electrode-array was carried out while the subject was awake. A test electrode was advanced into the periaqueductal grey matter through the posterior left thalamus. Sensory and motor testing were conducted uneventfully, indicating correct positioning, and the patient had no complaints. In particular, clinical oculomotor testing was normal. The test electrode was then replaced with the stimulating electrode-array. Shortly after the operation, the patient suddenly developed vertical diplopia, and was noted clinically to have a right hypertropia.

The stimulator was first tested on the day after implantation of the electrode-array. On stimulation through any of the 5 electrodes as cathode (*see below*), both eyes moved down. If either of the 2 lowest electrodes was used as cathode, the patient experienced a sensation of extreme dysphoria. Seven days after insertion of the electrode-array, it was withdrawn 8 mm. Stimulation, even with the lowest electrode as cathode, no longer produced dysphoria, but the hypertropia was not significantly improved.

At this point, the patient complained of vertical diplopia, with tilting of the 2 images with respect to each other, even with the stimulator off. He also noted that turning the stimulator on gave rise to a continuous perception of vertical movement. The stimulator produced a train of pulses of variable duration (controllable between 25 and 300 μs) and frequency (controllable between 20 and 100 Hz). There was a blocking capacitor in the output, so that no net direct current could be passed. The electrode-array consisted of 5 platinum electrodes, spaced 3.5 mm apart centre-to-centre. Each electrode was a cylinder of surface area 4.3 mm^2, except the lowest, which was of area about 4.0 mm^2 and which included a wire loop. The implant had provision for making any 1 electrode cathode, 3 of the 4 others being anodes in parallel. The pulse current was adjustable up to about 35 mA, but is known only roughly because the implant was inductively linked. The current at which effects were seen was probably about 20 mA at a pulse width of 100 μs, giving a charge density per pulse a little under 50 μCcm^{-2}. This makes no allowance for micro-roughness of the platinum which would have resulted in reduced current density. All observed effects seemed to be nearly independent of frequency over the range 20–100 Hz.

When the patient was walking, he noted vertical movement of the image from the right eye, but not of that from the left (i.e. he had oscillopsia from his right eye only). Neuro-ophthalmological assessment at this point revealed an acuity of 6/6 bilaterally, normal visual fields and fundi. Colour vision was normal (Ishihara, H–R–R charts, City University colour plates and the Farnsworth–Munsell 100 hue test). Pupils were 2 mm bilaterally and fully reactive to light and accommodation. There was no relative afferent defect.

The oculomotor findings at this stage were as follows. With the stimulator off, the patient exhibited a slight head tilt to the left. There was a right hypertropia in primary gaze (*see* Fig. 1A) and a torsional separation of the eyes of 5° (relative extorsion) as assessed on the synoptophore (*see* Table 1). His eyelid on the right was slightly higher than that on the left, consistent with the hypertropia. Vertical separation of the images decreased when the subject looked either up or down, but was worse when looking to the left. There was a full range of extra-ocular movement when each eye was tested separately. The vertical

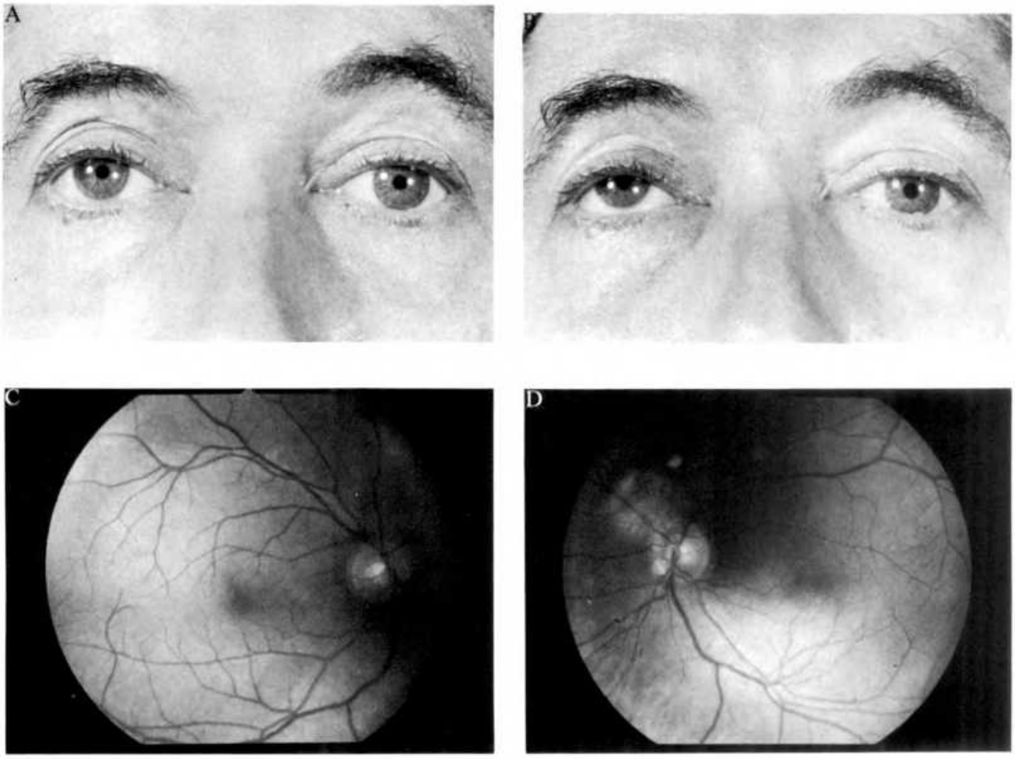


FIG. 1. A, photograph of patient's eyes with stimulator off. B, photograph with stimulator on. Subject is fixating with left eye and right eye elevates. C, right fundus. D, left fundus with stimulator off. Right fundus shows approximately 10° extorsion, left 15° extorsion.

TABLE 1. SYNOPTOPHORE OBSERVATIONS WITH STIMULATOR OFF.
NINE CARDINAL POSITIONS OF GAZE

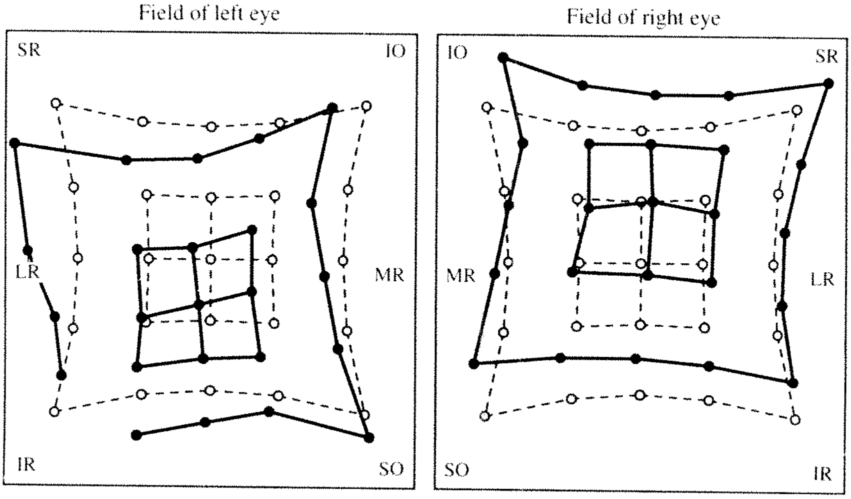
	Right	*Centre*	*Left*
Up	-3° R/L$^{4\Delta}$ Ext5°	-2° R/L$^{9\Delta}$ Ext5°	-2° R/L$^{13\Delta}$ Ext5°
Centre	-2° R/L$^{7\Delta}$ Ext5°	-2° R/L$^{11\Delta}$ Ext5°	-2° R/L$^{16\Delta}$ Ext5°
Down	$+3^\circ$ R/L$^{3\Delta}$ Ext8°	-2° R/L$^{10\Delta}$ Ext5°	-2° R/L$^{13\Delta}$ Ext5°

Each entry shows horizontal disparity in degrees (− = exo, + = eso), then vertical disparity in diopters and, finally, torsional disparity in degrees.

separation of the images subjectively decreased somewhat if the patient was tilted right ear-downwards, and increased in the left ear-downwards position.

When the stimulator was turned on, the right eye moved further up if the patient was fixating with his left eye (*see* Fig. 1B). There was an obvious torsional nystagmus affecting both eyes (fast phases counterclockwise when viewing the patient) which was more marked when the patient looked into the lower half of his field of gaze. Eye movements were still full. Vergence eye movements appeared relatively unimpaired with the stimulator on or off.

Testing with the Hess screen showed evidence of right hypertropia which was made markedly worse by turning the stimulator on (*see* Fig. 2). Fundus photography was performed with the stimulator off, using a KOWA fx-50R fundus camera. During photography of one eye, the other eye fixated an external target. In both eyes the maculae were lower than the discs, deviation from the horizontal (excyclotropia) being approximately 10° on the right and 15° on the left (*see* Fig. 1c, d). This was determined in each eye by comparing angulation relative to the horizontal of a line joining the centres of macula and optic disc.


A. Stimulator off

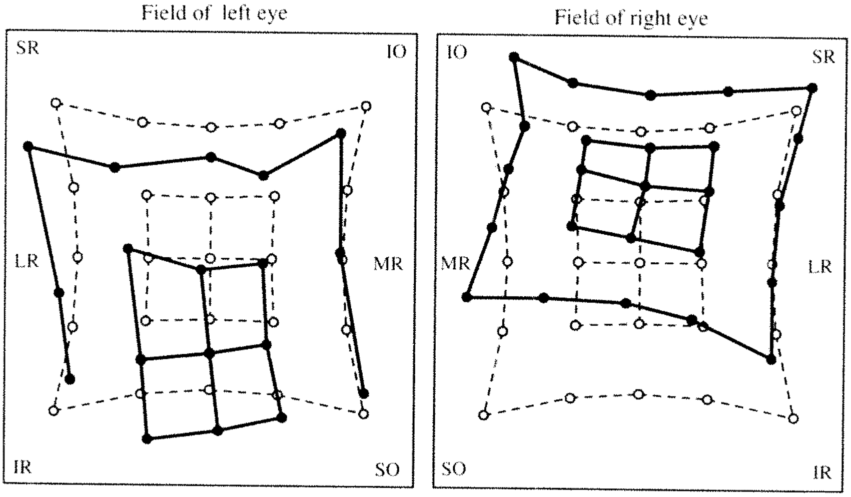

B. Stimulator on

Fig. 2. Hess chart (A) with stimulator off and (B) with stimulator on. IO: inferior oblique; IR: inferior rectus; LR: lateral rectus; MR: medial rectus; SO: superior oblique; SR: superior rectus.

ANATOMICAL LOCALIZATION

A CT scan performed before electrode withdrawal showed the electrode passing through the posterior thalamus on the left and terminating in the region just anterior to the right superior colliculus (*see* Fig. 3A). By projection of the stereotactic coordinates obtained during insertion of the electrode, the position of the electrode tip before withdrawal was 6 mm below and 6 mm behind the posterior commissure (PC) (by reference to the FM−PC plane) and 2 mm to the right of the midline. This is represented diagrammatically in Fig. 3B, and corresponds well to the CT image of Fig. 3A.

After withdrawal, a CT scan showed that the tip was located to the left of the midline (*see* Fig. 3C). Stereotactic coordinates confirmed this, as shown diagrammatically in Fig. 3D.

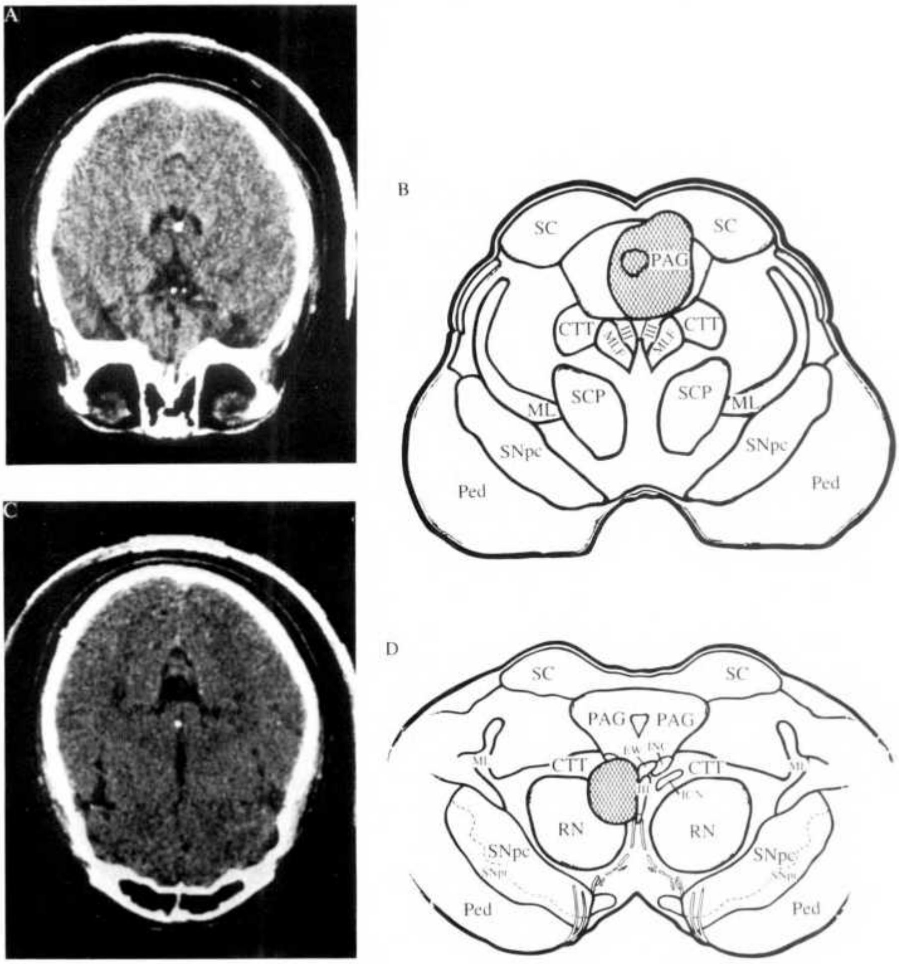


FIG. 3. A, CT scan showing transverse section at level of superior colliculus showing tip of electrode before withdrawal. The patient's right is the observer's right. B, diagram to show approximate position of electrode tip at this level. C, CT scan showing position of electrode tip after withdrawal, the scan slice being approximately 6 mm higher than in (A). D, diagram to show approximate position of electrode tip after withdrawal. CTT: central tegmental tract; EW: Edinger−Westphal nucleus; ICN: intracapsular nucleus; III: oculomotor nucleus; INC: interstitial nucleus of Cajal; ML: medial lemniscus; MLF: medial longitudinal fasciculus; PAG: periaqueductal grey; Ped: cerebral peduncle; RN: red nucleus; SC: superior colliculus; SCP: superior cerebellar peduncle; SNpc: substantia nigra, pars compacta; SNpr: substantia nigra, pars reticulata.

OCULOGRAPHY

Methods

Eye movements were recorded by means of DC-electro-oculography (EOG) and the magnetic scleral search coil (MSSC) technique (Robinson, 1963; Collewijn *et al.*, 1975). DC-EOG was used to assess the vestibulo-ocular reflex (VOR) in horizontal and vertical planes in the 2 eyes simultaneously. In assessing the vertical VOR, electrodes were placed over the upper and lower eyelids of each eye, and the calibrations for the 2 eyes were done independently. Stimulation was by passive horizontal and vertical head movements carried out by the examiner, whilst the patient attempted to fixate a cross on the wall 6 m away. Head movements were made at 2 frequencies (approximately 0.6 and 1.0 Hz).

Other eye movements were assessed using the MSSC technique. A coil which could record torsional movements in addition to vertical and horizontal ones (Collewijn *et al.*, 1985) was placed on the right eye. Saccades were tested initially, in both vertical and horizontal planes. The stimuli for this were red light-emitting diodes (LEDs) set into a tangent screen 150 cm from the subject. The LEDs were stepped pseudorandomly in step sizes ranging from 3.75° to 30°, with the interstep time interval varying from 1000 to 1400 ms to avoid predictability. Smooth pursuit was then tested. The stimulus for this was a moving circular spot (diameter 0.25°) of red laser light reflected off galvanometer-operated mirrors and tracing out a triangular waveform at 3 frequencies between 0.1 and 1.0 Hz. Optokinetic nystagmus was recorded during stimulation by a hand-held optokinetic drum rotated in all 4 planes. Fixation in the primary position was then studied with the stimulator on and off.

Data were recorded using a Mingograph chart recorder and analysed off-line. The exact details of the system used are described elsewhere (Tanyeri *et al.*, 1989). Analysis was performed by the use of a bit-pad digitizing tablet.

RESULTS

During fixation, the eyes were stationary if the thalamic stimulator was turned off. When it was turned on, a torsional nystagmus with an amplitude of about 2° became obvious in both eyes, and this continued until the stimulator was turned off, at which point it stopped abruptly (Fig. 4A). The fast phases of the nystagmus were counter-clockwise when viewing the patient from the front, and the slow phases were exponentially decreasing in waveform with a mean velocity of about $3^{\circ}s^{-1}$. Nystagmus was more pronounced in downgaze, but the direction was consistent throughout.

Examination of the VOR by EOG revealed that the excursion of the 2 eyes during head movement was different (*see* Fig. 4B). The right eye moved approximately 60% of the left. This was consistent with the fact that the patient noted that during head movement the image from the left eye appeared stationary but that from the right eye moved. The metrics of his saccades and smooth pursuit were within the normal range for this laboratory in both horizontal and vertical directions. Both vergence and optokinetic nystagmus to a hand-held drum were qualitatively normal.

DISCUSSION

The patient described here developed an ocular tilt reaction with right hypertropia, left head tilt and left-sided ocular extorsion, following insertion of a periaqueductal electrode, the tip of which was the right side of the midline. After withdrawal so that the electrode tip was now on the other side of the midline, the resting state remained unchanged, but turning the stimulator on caused an *exacerbation* of the tilt reaction initially produced by the destructive lesion.

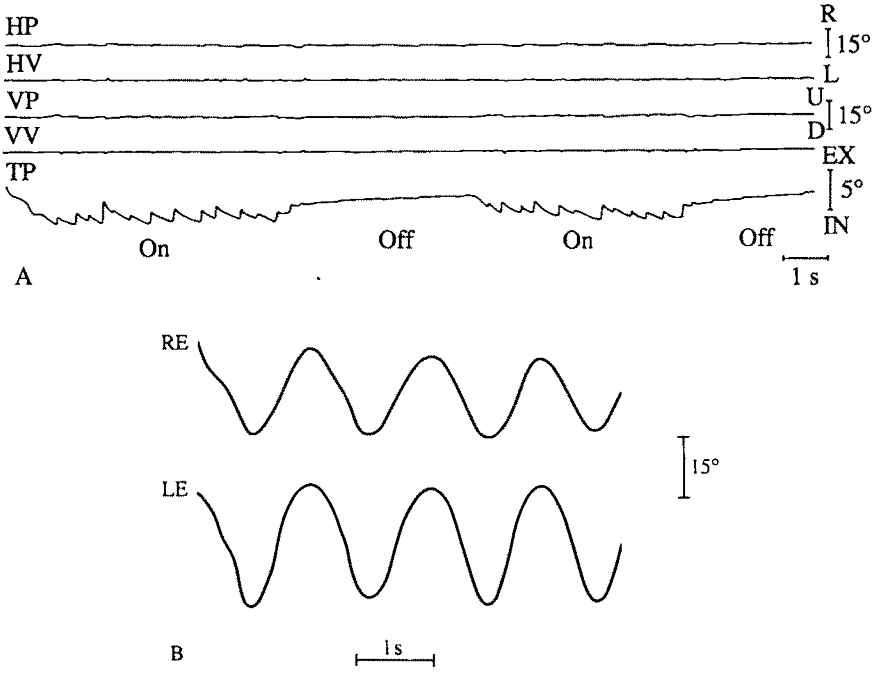


FIG. 4. A, right-eye recording using magnetic scleral search coil to show torsional nystagmus when the stimulator was turned on HP. horizontal position, HV: horizontal velocity, VP: vertical position, VV: vertical velocity, TP torsional position; R: right; L: left; U up; D: down, EX extorsion; IN: intorsion. For velocity channels, vertical-scale bar represents 60°/s B, DC-EOG recording to show difference in magnitude of vertical VOR between the 2 eyes LE left eye, RE right eye Up and down represent upward and downward eye movements, respectively.

Anatomical studies in experimental animals show that the utricle projects to the ipsilateral medial and inferior vestibular nuclei (Stein and Carpenter, 1967; Gacek, 1969). From here, projections relating to vertical eye movements pass principally to the contralateral trochlear nucleus and INC (Carleton and Carpenter, 1983). Presumably the fibres pass up in the contralateral medial longitudinal fasciculus (MLF), as do the fibres from the posterior semicircular canal (Graf *et al.*, 1983). Evidence for a direct, short-latency, pathway from the utricle to the contralateral trochlear nucleus has also been found (Baker *et al.*, 1973; Precht *et al.*, 1979). The fact that the pathways are crossed is consistent with the observed OTRs resulting from lesions and stimulation experiments, both in animals and in man.

In the cat, direct stimulation of the utricular nerve gives rise to a contralateral OTR, i.e. contralateral hypotropia, contralateral head tilt and contralateral ocular torsion (Suzuki *et al.*, 1969). In man, direct stimulation of the labyrinth due to the Tullio phenomenon has recently been reported to produce the same effect (Dieterich *et al.*, 1989). A similar picture is probably the case with paroxysmal (therefore presumably excitatory) lesions of the medulla (Rabinovitch *et al.*, 1977). Also consistent with this pattern, destructive lesions of the labyrinth (Halmagyi *et al.*, 1979) or medulla (Brandt and Dieterich, 1987) give rise to an ipsilateral OTR.

Laterality appears to be reversed with midbrain/diencephalic causes of the OTR.

Destructive lesions at this level give rise to contralateral OTR [Brandt and Dieterich, 1987 (Case 2); Waterston *et al.*, 1987 (Case 3); Halmagyi *et al.*, 1990], while paroxysmal (presumably excitatory) lesions give rise to ipsilateral OTR (Hedges and Hoyt, 1982). Thus, the utricular pathways in the brainstem must have crossed.

It is assumed that this case represents a pathological OTR. That the vertical separation of the images decreased with right ear-downwards position suggests an otolithic mechanism, but it should be noted that this finding is, in fact, unimportant to making the clinical diagnosis (Brandt and Dieterich, 1987). The findings are therefore consistent with the above crossed utricular pathway. A lesion at the level of the right superior colliculus gave rise to a contralateral (left-sided) OTR. After withdrawal, the electrode tip was on the other side of the midline (*see* Fig. 3A, C), and stimulation now gave rise to an ipsilateral (still left-sided) OTR.

During stimulation, the electrode tip was in the region of the INC (*see* Fig. 3D). Neurophysiological recording experiments suggest that the INC is involved in coordinating vertical eye and head movements (King *et al.*, 1981), and this is presumably related to the fact that it was the INC which Westheimer and Blair (1975*a,b*) stimulated in order to obtain the OTR in monkeys. Hyde and Eason (1959) also noted bilateral torsional movements after stimulation at a similar location in cats. This case probably represents the same phenomenon in man. It is presumed that the torsional nystagmus resulting from stimulation is mediated by the same mechanisms which mediate the OTR.

As mentioned in the Introduction, several reports of eye movements following brainstem electrical stimulation have been reported in man (Spiegel *et al.*, 1964; Nashold and Gills, 1967; Nashold, 1970; Nashold and Seaber, 1972; Sano *et al.*, 1972; Seaber and Nashold, 1980). In fact, during the surgical insertion of deep brain electrodes for relief of chronic pain, 'visual effects' (no further details are supplied by the authors) are quite common, though oculomotor causes for this are not specifically described (Ray and Burton, 1980). However, torsional nystagmus as a result of direct midbrain stimulation has not, to our knowledge, been previously described in man.

Interestingly, the torsional nystagmus which occurred as a result of stimulation implies that the rostral interstitial nucleus of the MLF (riMLF) was intact. The pre-saccadic generator for vertical eye movements is thought to be located in the riMLF (Büttner-Ennever *et al.*, 1982), and it has recently been shown in animals that torsional saccades are produced by the ipsilateral riMLF. A lesion of the riMLF produces a deficit of ipsilateral fast phases (Vilis *et al.*, 1989). The fact that this patient exhibited counter-clockwise fast phases implies that the right riMLF was intact and not lesioned by the original insult. The direction of the nystagmus also implies that it did not result from stimulation of the left riMLF, otherwise the nystagmus would have shown clockwise fast phases. The findings are consistent with left INC stimulation.

As described above, the excyclotropia of the left eye was expected as part of the OTR. The question arises as to whether the right eye was also in pathological excyclotropia. Excyclotropia is normal at a level of 3°–5° (Professor T. Brandt, personal communication), but the right-sided excyclorotation was greater than this. It could be argued that the usual cause of binocular extorsion is bilateral fourth nerve palsy, and that this therefore needs to be excluded. It is not likely to be the diagnosis in this patient for the following reasons. First, the separation of the images decreased on downgaze (*see* Table 1), looking both to the right and to the left. This would be most unexpected in a fourth nerve lesion, and the Hess chart (Fig. 2) is not suggestive of isolated superior oblique underactivity. Secondly, the torsional nystagmus of the left eye showed fast intorsional phases conjugate with those of the right, and not compatible with a significant degree of superior oblique palsy on that side. Thirdly, the electrode was never low enough in the brainstem to be near the fourth nerves or nuclei. If damage had occurred to an area large enough to affect these structures as a direct result of electrode placement, it ought to have been associated with obvious clinical signs, and a lesion such as a haemorrhage ought to have been visible on the CT scan.

Concerning the unexpected right-sided excyclotropia, it is noteworthy that, in addition to the extorsion, the patient suffered a uniocular disturbance of vertical VOR in that eye (*see* Fig. 4B). It is thus possible that there was a lesion of the supranuclear connections mediating both the vertical VOR and ocular torsion on that side, for example the connections from the INC to the trochlear or oculomotor nerve nuclei (Schwindt *et al.*, 1974; Steiger and Büttner-Ennever, 1979). Supranuclear uniocular elevation palsies have been described (Jampel and Fells, 1968; Lessell, 1975; Ford *et al.*, 1984), and, while this patient did not have any difficulty with elevation *per se*, it seems not unreasonable to suggest that a supranuclear lesion could have caused a right-sided tonic excyclotorsion and VOR disturbance. It is not certain that the right-sided excyclotorsion, while exceeding the normal range, was actually pathological. Even if it was, the mechanism was likely to have been separate from that of the underlying left-sided OTR.

In summary, the findings in this patient suggest that stimulation of, or in the region of, the INC in man gives rise to an OTR as it does in monkeys. The side of the OTR and the location of the electrode are consistent with the crossing of utricular pathways between medulla and midbrain previously suggested in the literature.

ACKNOWLEDGEMENTS

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REFERENCES

Baker R, Precht W, Berthoz A (1973) Synaptic connections to trochlear motoneurons determined by individual vestibular nerve branch stimulation in the cat. *Brain Research, Amsterdam*, **64**, 402–406.

Bennett AMH (1960) A stereotaxic apparatus for use in cerebral surgery. *British Journal of Radiology*, **33**, 343–351.

Brandt T, Dieterich M (1987) Pathological eye-head coordination in roll: tonic ocular tilt reaction in mesencephalic and medullary lesions. *Brain*, **110**, 649–666.

Büttner-Ennever JA, Büttner U, Cohen B, Baumgartner G (1982) Vertical gaze paralysis and the rostral interstitial nucleus of the medial longitudinal fasciculus. *Brain*, **105**, 125–149.

Carleton SC, Carpenter MB (1983) Afferent and efferent connections of the medial, inferior and lateral vestibular nuclei in the cat and monkey. *Brain Research, Amsterdam*, **278**, 29–51.

Collewijn H, van der Mark F, Jansen TC (1975) Precise recording of human eye movements. *Vision Research*, **15**, 447–450.

Collewijn H, Van der Steen J, Ferman L, Jansen TC (1985) Human ocular counterroll: assessment of static and dynamic properties from electromagnetic scleral coil recordings. *Experimental Brain Research*, **59**, 185–196.

DIETERICH M, BRANDT T, FRIES W (1989) Otolith function in man: results from a case of otolith tullio phenomenon. *Brain*, **112**, 1377–1392.

FORD CS, SCHWARTZE GM, WEAVER RG, TROOST BT (1984) Monocular elevation paresis caused by an ipsilateral lesion. *Neurology, Cleveland*, **34**, 1264–1267

GACEK RR (1969) The course and central termination of first order neurons supplying vestibular end organs in the cat. *Acta Oto-Laryngologica*, Supplement 254, 1–66.

GARELLI FF, GHERARDINI G (1972) Rapporti tra il nistagmo 'see-saw' e lo strabismo verticale 'sghembo' (skew-deviation): Descrizione di un caso. *Rivista di Neurologia*, **42**, 137–162

GOLDSTEIN JE, COGAN DG (1961) Lateralizing value of ocular motor dysmetria and skew deviation. *Archives of Ophthalmology*, **66**, 517–518.

GRAF W, MCCREA RA, BAKER R (1983) Morphology of posterior canal related secondary vestibular neurons in rabbit and cat. *Experimental Brain Research*, **52**, 125–138.

HALMAGYI GM, GRESTY MA, GIBSON WPR (1979) Ocular tilt reaction with peripheral vestibular lesion. *Annals of Neurology*, **6**, 80–83.

HALMAGYI GM, BRANDT T, DIETERICH M, CURTHOYS IS, STARK RJ, HOYT WF (1990) Tonic contraversive ocular tilt reaction due to unilateral meso-diencephalic lesion *Neurology, Cleveland*, **40**, 1503–1509

HEDGES TR, HOYT WF (1982) Ocular tilt reaction due to an upper brainstem lesion: paroxysmal skew deviation, torsion, and oscillation of the eyes with head tilt. *Annals of Neurology*, **11**, 537–540.

HYDE JE, EASON RG (1959) Characteristics of ocular movements evoked by stimulation of brainstem of cat. *Journal of Neurophysiology*, **22**, 666–678.

JAMPEL RS, FELLS P (1968) Monocular elevation paresis caused by a central nervous system lesion *Archives of Ophthalmology*, **80**, 45–57.

KEANE JR (1975) Ocular skew deviation: analysis of 100 cases. *Archives of Neurology, Chicago*, **32**, 185–190.

KEANE JR (1985) Alternating skew deviation: 47 patients. *Neurology, Cleveland*, **35**, 725–728.

KING WM, FUCHS AF, MAGNIN M (1981) Vertical eye movement-related responses of neurons in midbrain near interstitial nucleus of cajal. *Journal of Neurophysiology*, **46**, 549–562.

LESSELL S (1975) Supranuclear paralysis of monocular elevation. *Neurology, Minneapolis*, **25**, 1134–1136.

NASHOLD BS (1970) Ocular reactions from brain stimulation in conscious man. In: *Neuroophthalmology*, Volume 5. *Symposium of the University of Miami and the Bascom Palmer Eye Institute* Edited by J. L. Smith. St Louis: C. V. Mosby, pp. 92–103.

NASHOLD BS, GILLS JP (1967) Ocular signs from brain stimulation and lesions. *Archives of Ophthalmology*, **77**, 609–618.

NASHOLD BS, SEABER JH (1972) Defects of ocular motility after stereotactic midbrain lesions in man. *Archives of Ophthalmology*, **88**, 245–248.

PRECHT W, ANDERSON JH, BLANKS RHI (1979) Canal-otolith convergence on cat ocular motoneurons. *Progress in Brain Research*, **50**, 459–468.

RABINOVITCH HE, SHARPE JA, SYLVESTER TO (1977) The ocular tilt reaction: a paroxysmal dyskinesia associated with elliptical nystagmus. *Archives of Ophthalmology*, **95**, 1395–1398.

RAY CD, BURTON CV (1980) Deep brain stimulation for severe, chronic pain. *Acta Neurochirurgica*, Supplement 30, 289–293.

ROBINSON DA (1963) A method of measuring eye movement using a scleral search coil in a magnetic field. *IEEE Transactions on Bio-Medical Electronics*, **BME-10**, 137–145.

SANO K, SEKINO H, TSUKAMOTO Y, YOSHIMASU N, ISHIJIMA B (1972) Stimulation and destruction of the region of the interstitial nucleus in cases of torticollis and see-saw nystagmus. *Confinia Neurologica*, **34**, 331–338.

SCHWINDT PC, PRECHT W, RICHTER A (1974) Monosynaptic excitatory and inhibitory pathways from medial midbrain nuclei to trochlear motoneurons. *Experimental Brain Research*, **20**, 223–238

SEABER JH, NASHOLD BS (1980) Comparison of ocular motor effects of unilateral stereotactic midbrain lesions in man. *Neuro-ophthalmology*, **1**, 95–99.

SMITH JL, DAVID NJ, KLINTWORTH G (1964) Skew deviation. *Neurology, Minneapolis*, **14**, 96–105.

SPIEGEL EA, WYCIS HT, SZEKELY EG, SOLOFF L, ADAMS J, GILDENBERG P *et al.* (1964) Stimulation of Forel's field during stereotaxic operations in the human brain. *Electroencephalography and Clinical Neurophysiology*, **16**, 537–548.

STEIGER H-J, BÜTTNER-ENNEVER JA (1979) Oculomotor nucleus afferents in the monkey demonstrated with horseradish peroxidase. *Brain Research, Amsterdam,* **160,** 1–15.

STEIN BM, CARPENTER MB (1967) Central projections of portions of the vestibular ganglia innervating specific parts of the labyrinth in the rhesus monkey. *American Journal of Anatomy,* **120,** 281–317.

SUZUKI JI, TOKUMASU K, GOTO K (1969) Eye movements from single utricular nerve stimulation in the cat. *Acta Oto-Laryngologica,* **68,** 350–362.

TANYERI S, LUECK CJ, CRAWFORD TJ, KENNARD C (1989) Vertical and horizontal saccadic eye movements in Parkinson's disease. *Neuro-ophthalmology,* **9,** 165–177.

VILIS T, HEPP K, SCHWARZ U, HENN V (1989) On the generation of vertical and torsional rapid eye movements in the monkey. *Experimental Brain Research,* **77,** 1–11.

WATERSTON JA, STARK RJ, GILLIGAN BS (1987) Paramedian thalamic and midbrain infarction: the 'mesencephalothalamic syndrome'. In: *Clinical and Experimental Neurology. Proceedings of the Australian Association of Neurologists,* Volume 24. Edited by M. J. Eadie and C. M. Lander. Sydney: Williams and Wilkins, pp. 45–53.

WATKINS ES (1974) The place of neurosurgery in the relief of intractable pain. In: *Monographs in Anaesthesiology,* Volume I. *Relief of Intractable Pain.* Edited by M. Swerdlow. Amsterdam: Excerpta Medica, pp. 21–58.

WESTHEIMER G, BLAIR SM (1975*a*) The ocular tilt reaction—a brainstem oculomotor routine. *Investigative Ophthalmology and Visual Science,* **14,** 833–839.

WESTHEIMER G, BLAIR SM (1975*b*) Synkinese der Augen- und Kopfbewegungen bei Hirnstammreizungen am wachen Macacus-Affen. *Experimental Brain Research,* **24,** 89–95.

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CATEGORY-SPECIFIC NAMING AND COMPREHENSION IMPAIRMENT: A DOUBLE DISSOCIATION

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SUMMARY

We describe 2 neurologically impaired patients with lesions involving primarily the left temporal lobe, whose production and comprehension of words in the semantic category of animals were disproportionately *spared* in 1 case and disproportionately *impaired* in the other, in comparison to performance with other common categories. This double dissociation provides neurally based evidence for the view that lexical-semantic information is organized categorically.

INTRODUCTION

Research on language disorders that result from neurological impairment has helped to reveal the cognitive/linguistic mechanisms that underlie language processing. For example, performance by patients who are unable to produce orally the names of objects in response to pictures, despite preserved ability to write their names and preserved motor processes for producing speech, provide evidence for the functional and neural independence of mechanisms for accessing phonological representations of words from those mechanisms used for accessing the orthographic representations of the same words (Caramazza and Hillis, 1990). The detailed investigation of impaired language performance has not only served as the basis for postulating the major component processes that underlie tasks such as naming, but has also played a crucial role in revealing the internal structure of those components. Thus, for example, spared naming and comprehension of nouns in the presence of impaired naming and comprehension of verbs in some patients, and the opposite pattern by other patients, indicate that one of the organizing principles of the lexical system concerns the grammatical class of words (Miceli *et al.*, 1984; *see also* Caramazza and Hillis, 1991; McCarthy and Warrington, 1985; Miceli *et al.*, 1988; Zingeser and Berndt, 1988, 1990). Furthermore, within the class of nouns, patients may have preserved comprehension of abstract nouns along with impaired comprehension of concrete nouns, or the reverse pattern of performance, indicating that concreteness may be another important dimension in semantic processing (Warrington, 1981; Warrington and Shallice, 1984). A still finer organizational structure is indicated by a number of reports showing that naming and comprehension can be impaired in selective semantic categories of concrete nouns, such as animals, fruits and vegetables and so forth (Goodglass *et al.*, 1966; Warrington and McCarthy, 1983, 1987;

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Hart *et al.*, 1985; Basso *et al.*, 1988; Goodglass and Budin, 1988; McCarthy and Warrington, 1988; Semenza and Zettin, 1989; for reviews *see* Berndt, 1988; Shallice, 1988). However, the interpretation of these studies as providing evidence for the hypothesis that the semantic system is organized along the lines of such categories has been challenged, by contending that the observed category differences may reflect no more than differences in the degree of processing demands on the perceptual (or conceptual) system to distinguish between category members (Humphreys and Riddoch, 1987). In this paper, we report 2 patients whose patterns of naming and comprehension, with the same stimuli, were essentially mirror images of one another with respect to performance across categories. Because this double dissociation between categories in naming and comprehension cannot be accounted for by appealing to differences between categories in the degree of processing demands (Shallice, 1988), we argue that the cases provide evidence that it is the organization of semantic information that allows selective preservation or impairment of information in specific semantic categories.

CASE REPORTS

Patient J.J.

Social and medical history. J.J. is a 67-yr-old man who recently retired from an executive position with a large corporation. He completed high school and 2 yrs of college Four months prior to the initiation of this investigation, J.J. sustained a thromboembolic stroke. A CT scan 2 d post-onset revealed a large area of acute infarction in the left temporal lobe, and 2 focal infarcts in the left basal ganglia region: 1 involving the head of the caudate and another from the anterior limb of the internal capsule extending laterally into the putamen (Fig. 1). He exhibited no dysarthria, ataxia, or limb weakness. Visual field testing 11 mths later indicated very slight decrease on the right.

J J.'s past medical history is significant for insulin-dependent diabetes, hypertension and atrial fibrillation and is negative for alcohol consumption. He lives at home with his wife and is independent in activities of daily living, although he did not drive until nearly 1 yr after his stroke.

Clinical speech and language evaluation. J J. was referred to the Medical Rehabilitation Center of Maryland for outpatient language therapy 1 mth after his stroke. His spontaneous speech initially consisted of fluent, English jargon mixed with occasional phonemic paraphasias and neologisms, except for apppropriate social expressions. His performance on the Boston Diagnostic Aphasia Examination (BDAE; Goodglass and Kaplan, 1972) indicated profoundly impaired naming and comprehension of printed and

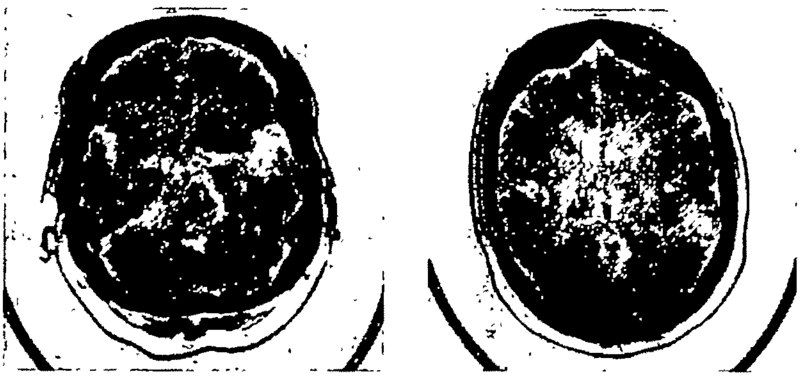

FIG. 1. CT scan of J.J., 2 d post-stroke.

auditory stimuli. Articulation, phonation and prosody were normal. J.J. failed to reach a basal level on the Peabody Picture Vocabulatory Test (PPVT). At 16 wks post-stroke, just prior to the experimental testing, he received a PPVT score of 114/175 (standard score of 62; percentile rank of 1) with auditory stimuli and 127/175 with printed stimuli. At the same time, although he had made significant improvement, performance on the BDAE indicated substantial, persisting impairments of comprehension and production of language, reflected in tasks of auditory word/picture matching (59/72 correct), following commands (7/15 points); understanding stories and a contextual questions (7/12 points); repeating phrases (1/16 correct), responsive naming (19/30); understanding printed sentences (6/10); and spelling to dictation (14/25) Spontaneous speech at the time was characterized by fluent, grammatical sentences with frequent circumlocutions and semantic paraphasias and rare phonemic errors. Oral reading was surprisingly good: he made only minor phonemic errors and morphological errors in oral reading of sentences and paragraphs. His score of 37/60 on the Revised Boston Naming Test (Goodglass and Kaplan, 1983) fell within the moderate range of severity. His score of 11/36 on the Modified Token Test (De Renzi and Faglioni, 1978) 6 mths after his stroke was in the 'severe' range of impairment. With printed stimuli, his score improved slightly, to 17/36. His age-corrected score of 33/36 on Raven's Coloured Progressive Matrices (Raven, 1962) was well above the normal mean of 29, consistent with intact visual perception and non-verbal reasoning.

Patient P.S.

Social and medical history. P.S. is a 45-yr-old, right-handed male who completed high-school and is currently president of a small contracting business. P.S. sustained brain injury from a severe blow to his head. CT scans immediately after the accident revealed subdural haematomas in both temporal lobes and a small, focal haematoma deep in the left frontal lobe. A right fronto-temporal epidural haematoma was evacuated by craniotomy. Recent CT scans, taken more than 2 yrs post-injury revealed a large area of damage in the left temporal lobe, and smaller areas in the right temporal and frontal lobes. As can be seen in Fig. 2, the primary locus of impairment, in the left temporal lobe, is more anterior than that of J.J., and has less superior extent

P.S. did not have any reduction of strength or sensation 1 mth after his accident. Visual fields were full. P S. was independent in all daily activities, including driving. He resumed working, in a limited capacity due to reading and writing deficits, 1 yr post-trauma. He did not suffer seizures during the time of the investigation.

Clinical speech and language evaluation. Four months after his brain injury, P.S.'s speech was entirely normal except for semantically related word substitutions (e.g. horse/cow) in selective categories. On formal testing, auditory comprehension was also normal, but comprehension was impaired for items that he could not name—animals and vegetables. Like J.J., P.S. exhibited flawless repetition of words and above average performance on the Wechsler Memory Scale visual memory subtest and on Raven's Coloured Progressive Matrices His primary difficulties were in the areas of reading and writing. His oral reading and spelling were similar to J.J 's, in that both patients made errors in oral reading and spelling-to-dictation that indicated use of sublexical procedures for converting print-to-sound and sound-to-print (e.g. in reading. *were* →

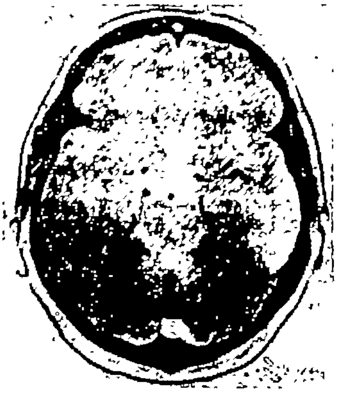

FIG. 2 CT scan of P S., 2 yrs post-trauma.

'we're'; *says* → /seɪz/, rhyming with *pays* by J.J. and *bear* → 'beer' and *mitten* /mət ɛn'/by P.S.; in spelling: SOFA → *soafa,* PARROT → *peret* by J.J.; OCTOPUS → *ockdipus*; TURTLE → *tertal* by P.S.) P.S. also made frequent visual errors in reading (e.g. *bread* → 'beard'); and his definitions of misread words indicated that he understood the word as his response rather than as the stimulus (e.g. *bread* → 'hair on your face').

EXPERIMENTAL INVESTIGATION

J.J.'s performance on the Boston Naming Test revealed a striking accuracy in naming pictures of animals, relative to other categories of comparable 'difficulty'. This dissociation was particularly conspicuous, because disproportionately *impaired* comprehension and production of words in the semantic category of animals has been reported (Sartori and Job, 1988; Silveri and Gainotti, 1988). It was also noted by P.S. that he had particular difficulty naming animals. Therefore, the following studies were designed to test lexical performance across categories for the 2 patients on the same stimuli.

Materials and procedure

Stimuli consisted of 144 items, from 10 semantic categories, matched for mean word length in letters and syllables. Two groups of 5 categories each were matched for surface and cumulative frequency. Mean surface frequencies for the 2 respective groups were 13.5–16.8 and 43.5–50.4. The list of 144 pictured objects were presented for oral naming once each session across 7 sequential sessions (over a period of 2 wks) to both J.J. and P.S. In order to compare performance across input and output modalities, the entire set of items was presented in separate sessions for oral naming, written naming, auditory word/picture verification, printed word/picture verification, oral reading and spelling-to-dictation. [Performance on reading and spelling-to-dictation will be reported only briefly here; *see* Hillis and Caramazza (1991*a*), for further details regarding the data and a possible interpretation.] Stimuli were presented in equal blocks of items for each task, in counterbalanced order, so that each item was presented only once (i.e. in only 1 task) in a single session.

Picture stimuli were black-and-white line drawings, with the exception of a few items that were coloured to distinguish them from related objects (e.g. lemon vs lime). Words were typed on separate cards for oral reading and printed word/picture verification tasks. Written responses that were recognizable as the target (e.g. LION → *lyon*) or as a semantically related item were scored as the intended word. For spoken word/picture verification, each word was presented 3 times, in 3 separate sessions, once with the corresponding picture, once with a semantically related picture and once with an unrelated picture. The subject received credit for the item only if his response to the word was correct with all 3 picture foils. The same procedure and scoring was followed for printed word/picture verification.

In the final study reported in this paper, the patients were presented with the name of each stimulus, and were instructed to define it as completely as possible. Responses were recorded and independently scored by 2 examiners, 1 of whom was naive to the purpose and to the hypothesis that had been formulated in the study. Interjudge reliability between scorers was 93.8%, so only the scores of the naive judge are reported.

RESULTS

Category effects

Table 1 shows the substantial advantage for animals over other categories (e.g. furniture, foods, etc.; *see* Fig. 3) in J.J.'s oral naming performance, and the opposite pattern by P.S., at 4 mths post-injury for each patient. For P.S., performance on the category 'vegetables' is reported separately, because his impairment was as severe for 'vegetables' as it was for 'animals' (whereas for J.J., 'animals' and not 'vegetables' were selectively spared). It is clear from inspection of the results that the opposing dissociations between categories were remarkably stable.

In order to identify the processing component in which the effect arose, performance on the same stimuli were compared across oral and written naming and spoken and written word/picture verification. These tasks were given at 6 mths post-onset; some were repeated 7 mths later.

J.J.'s oral naming for land animals, water animals and birds ranged from 77 to 100% correct, compared to 8–33% correct for non-animal categories ($\chi_1^2 = 67.78$; $P < 0.001$; Table 2). Similar differences favouring animals over non-animals were exhibited in written naming ($\chi_1^2 = 39.49$; $P < 0.001$), spoken word/picture verification ($\chi_1^2 = 12.29$; $P < 0.001$) and written word/picture verification ($\chi_1^2 = 61.32$; $P < 0.0001$). There was no difference in accuracy between categories with high frequency items and categories with mid-frequency items for any task (e.g. 30.5% vs 35.5% correct, respectively, for oral naming).

TABLE 1 PERCENT CORRECT ORAL NAMING OVER 7 ADMINISTRATIONS

J.J.	*n*	*1*	*2*	*3*	*4*	*5*	*6*	*7*
All animals	*46*	91	85	72	80	76	74	92
Non-animals	*98*	12	14	14	11	12	7	17
P.S.								
All animals	*46*	39	39	39	41	37	48	72
Vegetables	*12*	25	25	25	25	33	33	42
All other	*86*	88	91	91	92	94	93	95

TABLE 2 ACCURACY RATES ACROSS CATEGORIES AT 6 MTHS POST-BRAIN DAMAGE

	n	*Oral naming*	*Written naming*	*Spoken word/picture verification*	*Printed word/picture verification*
J.J					
All animals	*46*	91.3	70.0	91.3	97.8
All others	*98*	20.4	15.3	60.2	42.9
P.S.					
All animals	*46*	39.1	34.8	93.5	89.1
Vegetables	*12*	25.0	33.3	91.7	83.3
All others	*86*	89.5	76.7	100	83.7

On the same set of items, subject P.S. named animals with significantly *lower* accuracy than items in all of the other categories combined, excluding vegetables ($\chi_1^2 = 29.05$; $P < 0.001$ for oral naming; $\chi_1^2 = 15.75$; $P < 0.001$ for written naming). P.S. made spoken word comprehension errors only in the animal and vegetable categories. For both patients, error rates were lower in the spoken word comprehension task than in the naming task, presumably because a correct response in word/picture verification does not require complete semantic information. For P.S., written word comprehension was poorer than spoken word comprehension, particularly in categories other than animals and vegetables, because he made visual errors in all categories of words (e.g. accepted *waist* for a picture of a wrist). Hence, category discrepancies in accuracy were masked by these additional errors in otherwise 'spared' categories. However, as discussed further below, P.S. made semantic errors in printed word/picture matching only in animal and vegetable categories. It may also be worth noting that performance on 'fruits' and 'transportation' was better than other non-animal categories for J.J. and worse than non-animal/vegetable categories for P.S. The possible implications of this observation are taken up in the general discussion.

Retesting 7 mths later, when the patients language performance had improved, showed that the category-specific effect was still present. J.J. correctly named all animals, but only 58–70% of items in all other categories but transportation (Fig. 3). The difference in accuracy between animal and non-animal categories was still highly significant ($\chi_1^2 = 11.81$; $P < 0.001$). J.J. made no errors in response to any animal names in spoken word/picture verification, but incorrectly accepted 19.3% of the semantically related pictures for the other categories. The opposite pattern of naming impairment in P.S. also persisted ($\chi_1^2 = 38.71$; $P < 0.001$ for animals vs non-animals, excluding vegetables). He was not retested on the word/picture verification tasks.

Error types

The types of errors made by J.J. and P.S. were similar across the tasks reported here, and were similar for the 2 patients. Table 3 includes examples of errors across tasks, and illustrates that semantic errors occurred in opposite categories for the 2 patients. Error types are described in further detail below, for each task separately.

Picture naming. J.J. correctly named 57% of the 144 pictures. His oral naming errors were most often semantic paraphasias (65% of errors; 28% of responses). The majority of these errors were within-category confusions, such as BOAT → 'motorcycle', which

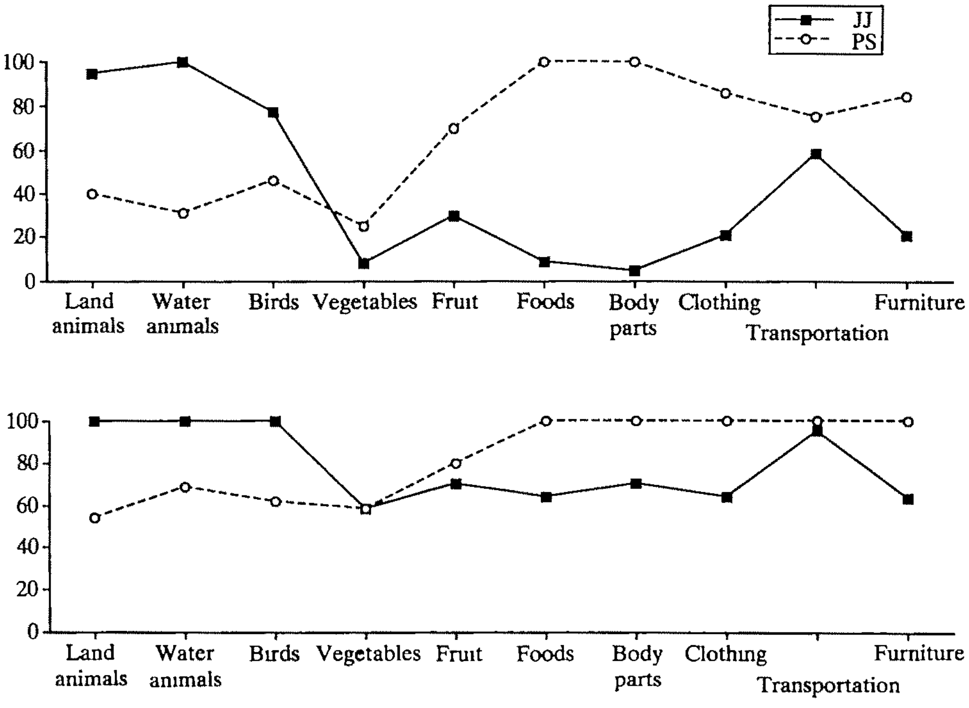

FIG. 3 Percent correct oral naming as a function of category at 6 mths post-onset (*top*) and 13 mths post-onset (*bottom*)

have a 'coordinate' relationship to the target; but a few responses were superordinate labels, such as 'motor vehicle' for TRUCK or other associated words (e.g. BUREAU → 'shoe box'). J.J. also produced some neologisms (4% of responses), circumlocutions (3% of responses), apparently unrelated words (7% of responses) and omissions ('don't know' responses; < 1%). P.S. correctly named 68% of the pictures. All of P.S.'s oral naming errors were coordinate semantic errors (SEAL → 'mouse', 13% of responses) or circumlocutions (e.g. VASE → 'flower holder'; 19% of responses).

Written naming. The majority of each patient's responses in written naming were

TABLE 3 EXAMPLES OF ERROR TYPES ON EACH TASK BY J J AND P S FOR IMPAIRED AND INTACT CATEGORIES

Stimulus	*Oral naming*	*Written naming*	*Spoken word/picture verification*	*Written word/picture verification*
J.J.				
Animals				
Shark	+	+	+	+
Crab	+	+	+	+
Donkey	+	+	+	+
Parrot	+	+	+	+
Bear	+	+	+	+
Ostrich	+	+ (Ostrage)	+	+
Whale	+	+	+	+
Alligator	+	+	+	+
Kangaroo	+	+ (Cangoro)	+	+
Squirrel	+	+ (Squirel)	+	+
Non-animals				
Elbow	Knee	Hand	Wrist	Hand
Bench	Chair	+	Chair	Drawer
Cherry	Grape	Plumb	Grape	+
Sweater	Jacket	Jacket	Coat	Jacket
Apricot	Pear	Pears	+	Berry
Shirt	Silk dressing	Coate	Pants	Sweater
Drawer	Serving device	Vase	+	Chair
P S.				
Animals				
Dolphin	Flipper	nr	Pelican	Pelican
Kangaroo	Giraffe	nr	+	+
Shark	Whale	Waile	Whale	+
Walrus	Clam	Seal	Seal	Seal
Parrot	S American Bird	Bird	Penguin	Penguin
Vegetables				
Carrot	Onion	Cyoucumber	Cucumber	+
Bean	Peas	Pea	Pea	Pea
Other				
Drawer	+	+ (Dror)	+	+
Jacket	+	+ (Gaket)	+	+
Elbow	+	+	+	+
Bench	+	+	+	+
Helicopter	+	+ (Helacopter)	+	+
Sweater	+	+ (Sweter)	+	+

+ = correct response (with patient's spelling, if not accurate, in parentheses) nr = no response or 'don't know' recognizable either as the correct word (e.g. WHALE → *whayle;* LEMON → *lemmun*; 33% of responses by J.J.; MOTORCYCLE → *motor ciekil;* 85% of responses by P.S.) or as a semantic paragraphia (e.g. TOE → *hand*; 58% of responses by J.J.; SHARK → *waile*; 8% of responses by P.S.). The remaining errors were unrecognizable misspellings or 'don't know' responses (8% of responses for J.J.; 6% for P.S.) or unrelated words (e.g. UMBRELLA → *window*; 1% for each). When recognizable spellings are scored as the intended word, the pattern of errors in written naming is similar to the pattern of errors in oral naming of each patient, except that pictures that elicited circumlocutions in oral naming often elicited in written naming semantic paragraphias in J.J.'s case and recognizably correct written names in P.S.'s case. It is quite possible that P.S. would have produced correct oral names for these items following each circumlocution if he had been given additional time (although not formally timed, written naming responses appeared to be more delayed than oral naming responses. Further, P.S. was unlikely to produce circumlocutions—which tend to be lengthy—in writing, because he found writing to be difficult.)

Word/Picture correspondence tasks. Errors in auditory word/picture verification matching tasks by both patients were limited to within-category items. That is, neither patient accepted or selected a semantically unrelated word for any of the picture stimuli. Furthermore, neither patient ever rejected a correct word/picture match. In printed word/picture matching, neither patient accepted words that were phonologically but not visually similar to the name of the picture (e.g. cherry/chair), but P.S. frequently accepted a word that was visually similar to the name of the picture (e.g. bear/bean). These visual errors account for the higher error rates by P.S. in printed word comprehension tasks, especially in categories other than animals and vegetables. In the latter categories, he made primarily semantic errors; for example, he accepted a picture of a dolphin for the word *pelican* and accepted a picture of a walrus as the referrent of *seal*. The presence of semantic errors in printed word comprehension, restricted to the categories of animals and vegetables, is consistent with a single impaired mechanism underlying semantic errors in comprehension and naming tasks, in addition to a more peripheral problem that led to visual errors in all categories.

Although it will not be discussed in detail here, P.S.'s difficulty recognizing printed words was also reflected in his oral reading—he made many phonologically plausible errors (e.g. *drawer* → [draɚ]) as well as visual errors (e.g. *beard* → 'bread') in reading words from all categories, in addition to semantic errors (e.g. *deer* → 'bear'; *pea* → 'beet') that occurred primarily in the categories of animals and vegetables. Together with his pattern of performance in the printed word comprehension task, these errors indicated an impairment in accessing the orthographic representation of words in all categories, in addition to the impairment that gave rise to semantic errors on animals and vegetables in all lexical tasks (*see* Hillis and Caramazza, 1991*b*, for additional information on P.S.'s reading). His performance in spelling-to-dictation was similar to oral reading in that his most common errors were phonologically plausible misspellings of the stimulus (e.g. 'carrot' → *cairit*, 'kangaroo' → *cangarue*). Thus, the fact that semantic errors were less frequent in oral reading and dictation than in naming tasks, can be accounted for by assuming that P.S. ordinarily accomplished the former tasks—correctly or incorrectly—via sublexical procedures for converting print-to-sound or sound-to-print.

J.J.'s performance in reading and spelling is discussed in detail in a separate paper (Hillis and Caramazza, 1991*a*). Here we simply note that in oral reading he was 100% correct for animals and 86–100% correct for non-animal categories. Essentially all of his errors were phonologically plausible responses or both semantically and visually related words (e.g. *waist* → 'wrist'). Spelling-to-dictation was very similar to written naming performance at 6 mths post-stroke, but far exceeded naming and comprehension tasks by 13 mths post-stroke. The majority of his errors were phonologically plausible misspellings (e.g. 'mustache' → *mustash*). However, many of his correct responses on the later administration of the task could not be accounted for on the basis of semantic information—which was shown to be impaired for the same items at the same time in word/picture matching tasks—nor on the basis of sublexical information alone (since he correctly read and spelled some irregular words that elicited errors in the comprehension tasks). This pattern of performance may be explained by assuming that J.J. can access lexical-orthographic and lexical-phonological representations on the basis of *combined* input from the semantic system and the sublexical conversion mechanisms—neither of which could alone support accurate selection of the target representation.

Comprehension tasks

In order to more fully assess J.J.'s and P.S.'s word comprehension performance, they were asked to define sets of spoken words. This assessment took place 13 mths after each patient's brain damage; by this time, J.J.'s connected speech had improved sufficiently for him to convey his understanding of stimulus words.

J.J. defined the 144 words that had been used in the earlier tasks. All of his definitions of animals were judged to be accurate by 2 scorers. For example, he defined 'mouse' as 'A small little animal with a pointed nose, pointed ears, and a little snout; about 1 inch high, or 1¼ inches. It doesn't have much value, except that it can be eaten by animals. Cats chase them. It eats whatever it can steal in people's houses, even in my house. They move rather quickly, climb up on things, and can stand on two feet.' In contrast to his performance in defining animals words, 15.3% of his definitions of non-animal names were scored as 'clearly wrong' and 8.2% as ambiguous. The definitions scored as errors were either specific descriptions of some object other than the stimulus (such as: *bench* → 'A device you sit on, about 12 inches high with 4 legs. It revolves you around while sitting. Can be made of metal or wood') or acknowledgement of his lack of understanding of the word (such as: *apricot* → 'I don't remember. I've heard of it. It's a fruit, but I don't remember which one. That's strange. I suppose it's sweet.'). Additional examples of his definitions are reported in Table 4.

P.S. defined 70 names of animals and vegetables and 70 names of objects in the other categories previously tested, matched for word frequency. He resolved any ambiguity in his definitions by giving additional information upon request. Responses to 15.7% of animal and vegetable names were wrong. As was the case for J.J., some of P.S.'s error responses indicated that he understood the word as a related item (e.g. he defined 'artichoke' thus: 'Looks like a pear; has a big seed in it'), but most indicated that he accessed minimal, if any, semantic information (e.g. 'leek' was defined as, 'An animal, I've heard of them'). All of P.S.'s responses to words from all other categories were accurate (Table 4).

TABLE 4 DEFINITIONS OF ITEMS IN IMPAIRED AND UNIMPAIRED CATEGORIES

J.J.	
Animals	
Lion	'A large animal, about 4 feet tall, maybe taller at the shoulders; it has a long body and very large paws, and stands on all four legs. It has a monstrous head with which it growls; and it has a mane—a large body of hair. It lives in Africa.'
Heron	'This bird has a long neck and legs It lives near water. Stands in the water. very tall—maybe about 6 feet Not brown, but white and blue perhaps '
Non-animals	
Celery	'Very white-bodied meat soft ..easy to eat '
Melon	'I'm not sure It's a fruit, a soft material I don't remember if it is yellow or green or orange I've forgotten too many things '
Drawer	'Something that has to be drawn—pictures.'
P S.	
Animals and vegetables	
Heron	'A fish.'
Salamander	'Sounds familiar a fish?'
Aardvark	'Has a duck face that hangs down, a bird that can't fly.'
Brussel sprouts	'Like rice. You put meat on them '
Pinto beans	'I don't know... sounds Mexican '
Celery	'Turns yellow if you leave it too long You steam it and pour melted cheese on it. I don't know if you can eat it raw or not '
Other	
Apricot	'Like a peach, only smaller You can buy them canned or dried or fresh.'
Ottoman	'A chair without a back, that you put your feet on.'

DISCUSSION

J.J.'s ability to name a picture was dependent on the semantic category of the pictured item. He made many more semantic errors in response to items that are not animals than in response to animal stimuli. P.S. showed the opposite pattern: more semantic (and other) errors in response to animals than to non-animal categories. There are 4 important aspects to the reported results: (1) in both patients, the deficit involved both naming and comprehension, and was independent of the form of input—pictures and aurally presented words—and the form of output—written and oral naming; (2) semantic errors were the predominant error type in all of these tasks; (3) the impairment was not uniform across semantic categories, but was restricted to certain categories in each patient; and (4) the semantic categories impaired in the 2 patients were mirror images of each other—a double dissociation.

This double dissociation between categories would seem to indicate that the sort of information that distinguishes members of 1 category from another is an important dimension of the processing structure of at least 1 component of the complex system of naming. Because the impairment involved both comprehension and production, and the errors were predominantly within-category semantic confusions (facts 1 and 2, *above*), the likely locus of damage is to the semantic component of the word processing system. Furthermore, the similar types of errors in oral and written picture naming and word/picture verification (mostly semantic coordinates of the target), and comparable degrees of category effects across tasks suggest that the errors in these 3 tasks have a common source. The only components of the lexical processing system that are common to all picture naming and comprehension tasks are visual/perceptual mechanisms and the semantic component (*see* Fig. 4). However, the fact that both J.J. and P.S. had category specific impairments in defining auditorily presented words rules out a visual-perceptual basis for the naming and comprehension errors. Therefore, the observed category-specific effects (facts 3 and 4, *above*) are most plausibly assumed to result from damage to the semantic component.

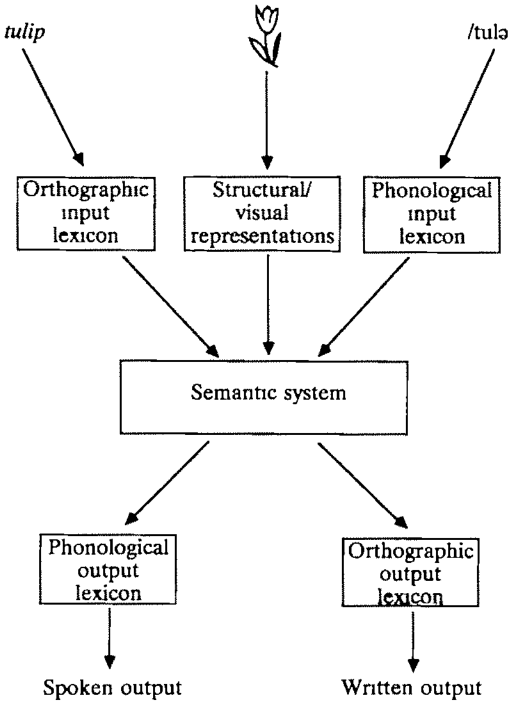
tulip
/tuləp/
Orthographic input lexicon
Structural/ visual representations
Phonological input lexicon
Semantic system
Phonological output lexicon
Orthographic output lexicon
Spoken output
Written output

FIG 4. A model of the cognitive processes that underlie naming and comprehension of words

The reported results cannot be accounted for by the hypothesis that the observed category differences may be attributable to perceptual characteristics of the categories in question, such as the degree of perceptual (or conceptual) overlap between members of a given category. Humphreys and Riddoch (1987) have argued, for example, that the high degree of perceptual overlap among animals (4 legs, a head and so on), may account for the disproportionately impaired naming and recognition of animals reported for several other patients described in the literature (Sartori and Job, 1988; Silveri and Gainotti, 1988), because of the greater toll placed on the perceptual system to discriminate between members of this category. Consistent with this explanation, the authors reported a patient, J.B., who exhibited greatest difficulty naming items in categories with a high degree of contour overlap and perceptual similarity (Riddoch and Humphreys, 1987). Irrespective of the adequacy of their account for J.B., this proposal cannot explain J.J.s category effects: his naming was *least* impaired in the categories that presumably require the most difficult perceptual discrimination. Nor can the category effects be explained as reflections of differences in premorbid familiarity with certain categories. J.J. denied a particular interest in animals; his main avocations were carpentry and mechanics. Interestingly, it was P.S. who reported a special interest in animals: he watched television documentaries about animals, hunted and visited wildlife reservations.

In conclusion, the fact that circumscribed neurological damage can affect some semantic categories and not others supports the hypothesis that information in the semantic component is organized by semantic categories such as 'animals', 'vegetables' and so forth. This leaves open the questions of the proper inventory of semantic categories and of the functional and neural principles that determine category structure. On the latter issue, there are at least 2 alternative accounts that may be offered. In one view, word meanings consist of undifferentiated holistic descriptions with category related items neurally represented contiguously, such that damage to a particular region of the brain will tend to affect members of the same category. An alternative account, that is consistent with other results on semantic processing in other cases (Warrington and McCarthy, 1987; Caramazza and Hillis, 1990; Hillis *et al.*, 1990) is that a semantic representation consists of a set of functional and perceptual features, some of which are common to members of the same category (Miller and Johnson-Laird, 1976; Jackendoff, 1983). On this hypothesis, the semantic representations of related items, say, of DOG <animate, domestic, 4-legged, furry, omnivorous... > and CAT <animate, domestic, 4-legged, furry, carnivorous... >, would consist of overlapping subsets of semantic features, such that damage to some of these features would affect a number of related items. Thus, for example, damage to the features <domestic>, <furry> and <carnivorous> would impede normal processing of the semantic representations of words in the category of animals. Damage to individual semantic features may also account for the fact the damage to 2 or more categories frequently co-occur. For instance, a number of previously reported patients have shown a discrepancy in performance for animate vs inanimate categories (Warrington, 1981; Warrington and Shallice, 1984; Basso *et al.*, 1988; McCarthy and Warrington, 1988), which might be expected if they were differentially impaired in processing one or more features common to the semantic representations of living things. Further, it is interesting to note in this context that patient J.J., who presented with no difficulty in comprehending and producing words in the semantic category of animals, also showed relatively good performance for the transportation category; and that the opposite pattern obtained for the other patient (P.S.). This result invites the speculation that the observed association is not purely accidental but may, instead, reflect the relative sparing or damage of a semantic feature common to the animal and transportation category—perhaps motility.

One possible instantiation of the 'common features' hypothesis has been put forward by Damasio (1990), who proposed that particular neural regions are dedicated to specific sensory 'feature fragments', such as features of an object's physical structure (shape, colour, etc.), operations in space, and value to the perceiver (other aspects of Damasio's proposal, such as representation of combinatorial codes and feedback/feedforward systems are not relevant to the present issue). Damasio contended that neural organization thus reflects features that define entities, but that these features do *not* correspond to boundaries of conceptual categories like 'animals', 'vegetables', etc., but rather, to subgroups within and across categories. Although this conclusion is consistent with many reports of category-influenced performance by brain-damaged patients, the relative specificity of

J.J.'s preservation of the category of 'animals', especially during the latter period of his recovery, indicates that the proposed features represented in specific regions of the brain would necessarily correspond more closely than proposed by Damasio to features that characterize certain conceptual categories.

Independently of whether the 'holistic representation' account or 'featural representation' account, or some other, ultimately proves to be the correct one, the reported double dissociation of category-specific semantic deficits indicates that word meanings are organized in the brain by semantic categories.

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REFERENCES

Basso A, Capitani E, Laiacona M (1988) Progressive language impairment without dementia: a case with isolated category specific semantic defect. *Journal of Neurology, Neurosurgery, and Psychiatry,* **51,** 1201–1207.

Berndt RS (1988) Category-specific deficits in aphasia *Aphasiology,* **2,** 237–240.

Caramazza A, Hillis AE (1990) Where do semantic errors come from? *Cortex,* **26,** 95–122.

Caramazza A, Hillis AE (1991) Lexical organization of nouns and verbs in the brain. *Nature,* **349,** 788–790.

Damasio AR (1990) Category-related recognition defects as a clue to the neural substrates of knowledge *Trends in Neurosciences,* **13,** 95–98.

De Renzi E, Faglioni P (1978) Normative data and screening power of a shortened version of the Token Test. *Cortex,* **14,** 41–49.

Goodglass H, Klein B, Carey P, Jones K (1966) Specific semantic word categories in aphasia. *Cortex,* **2,** 74–89.

Goodglass H, Kaplan E (1972) *The Boston Diagnostic Aphasia Examination* Philadelphia, PA: Lea and Febiger.

Goodglass H, Kaplan E (1983) *Boston Naming Test* Second edition. Philadelphia: Lea and Febiger.

Goodglass H, Budin C (1988) Category and modality specific dissociations in word comprehension and concurrent phonological dyslexia. *Neuropsychologia,* **26,** 67–78.

Hart J, Berndt RS, Caramazza A (1985) Category-specific naming deficit following cerebral infarction. *Nature, London,* **316,** 439–440.

Hillis AE, Rapp B, Romani C, Caramazza A (1990) Selective impairment of semantics in lexical processing. *Cognitive Neuropsychology,* **7,** 191–243.

Hillis AE, Caramazza A (1991*a*) Mechanisms for accessing lexical representations for output: evidence for a category-specific semantic deficit. *Brain and Language,* **40,** 106–144

Hillis AE, Caramazza A (1991*b*) The reading process and its disorders. In: *Cognitive Neuropsychology in Clinical Practice.* Edited by D. Margolin. New York: Oxford University Press. In press.

Humphreys GW, Riddoch MJ (1987) On telling your fruit from your vegetables: a consideration of category-specific deficits after brain damage. *Trends in Neurosciences,* **10,** 145–148.

Jackendoff R (1983) *Semantics and Cognition* Cambridge, MA: MIT Press

McCarthy RA, Warrington EK (1985) Category specificity in an agrammatic patient: the relative impairment of verb retrieval and comprehension. *Neuropsychologia,* **23,** 709–727.

McCarthy RA, Warrington EK (1988) Evidence for modality-specific meaning systems in the brain *Nature, London,* **334,** 428–430.

MICELI G, SILVERI MC, VILLA G, CARAMAZZA A (1984) On the basis for the agrammatic's difficulty in producing main verbs. *Cortex*, **20**, 207–220.

MICELI G, SILVERI MC, NOCENTINI U, CARAMAZZA A (1988) Patterns of dissociation in comprehension and production of nouns and verbs. *Aphasiology*, **2**, 351–358.

MILLER GA, JOHNSON-LAIRD PN (1976) *Language and Perception.* Cambridge, MA: Harvard University Press.

RAVEN J (1962) *Coloured Progressive Matrices.* London: H. K. Lewis.

RIDDOCH MJ, HUMPHREYS GW (1987) Visual object processing in optic aphasia: a case of semantic access agnosia. *Cognitive Neuropsychology*, **4**, 131–185.

SARTORI G, JOB R (1988) The oyster with four legs: a neuropsychological study on the interaction of visual and semantic information. *Cognitive Neuropsychology*, **5**, 105–132.

SEMENZA C, ZETTIN M (1989) Evidence from aphasia for the role of proper names as pure referring expressions. *Nature, London*, **342**, 678–679.

SHALLICE T (1988) *From Neuropsychology to Mental Structure.* Cambridge· Cambridge University Press.

SILVERI MC, GAINOTTI G (1988) Interaction between vision and language in category-specific semantic impairment. *Cognitive Neuropsychology*, **5**, 677–709.

WARRINGTON EK (1981) Neuropsychological studies of verbal semantic systems. *Philosophical Transactions of the Royal Society of London*, **B295**, 411–423.

WARRINGTON EK, McCARTHY R (1983) Category specific access dysphasia. *Brain*, **106**, 859–878.

WARRINGTON EK, SHALLICE T (1984) Category specific semantic impairments. *Brain*, **107**, 829–853.

WARRINGTON EK, McCARTHY RA (1987) Categories of knowledge: further fractionations and an attempted integration. *Brain*, **110**, 1273–1296.

ZINGESER LB, BERNDT RS (1988) Grammatical class and context effects in a case of pure anomia· implications for models of language production. *Cognitive Neuropsychology*, **5**, 473–516.

ZINGESER LB, BERNDT RS (1990) Retrieval of nouns and verbs in agrammatism and anomia. *Brain and Language*, **39**, 14–32

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COGNITIVE IMPAIRMENT IN EARLY, UNTREATED PARKINSON'S DISEASE AND ITS RELATIONSHIP TO MOTOR DISABILITY

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SUMMARY

Current knowledge of cognitive dysfunction in Parkinson's disease (PD) has largely been obtained from studies of chronically treated patients in whom effects of disease chronicity, treatment, depression and dementia are confounding factors. Studies of untreated patients have examined few cognitive domains and relationships between cognition, depression and motor disability have been incompletely explored. Accordingly, we studied 60 consecutive patients with newly diagnosed, untreated, idiopathic PD and 37 matched, healthy control subjects; no subject had clinical dementia or depression. All subjects received tests of specific processes of memory and cognition, including working memory, verbal and non-verbal short- and long-term memory, language, visuospatial capacity, set-formation and shifting and sequencing. Patients also received quantitative global clinical measures of severity of dementia, depression and motor disability. The PD group as a whole showed deficits in immediate recall of verbal material, language production and semantic fluency, set-formation, cognitive sequencing and working memory and visuomotor construction. However, this group was unimpaired in immediate memory span, long-term forgetting, naming, comprehension and visual perception. Language deficits and more severe frontal lobe impairments were confined to those PD patients scoring abnormally on a Mini Mental State examination. Motor disability correlated strongly with severity of depression but weakly with cognitive impairment. Cognitive sequencing, set-formation and set-shifting deficits tended to associate with depression, but otherwise there was no association between cognition and depression. The results indicate dissociation of cognition and motor control in early PD which suggests that cognitive dysfunction is largely independent of frontostriatal dopamine deficiency underlying motor disability. Some, but not all, of the frontal lobe deficits of chronic disease are detectable in early, untreated PD. The pathogenesis of the cognitive deficits shown here appears to involve extrastriatal dopamine systems or non-dopaminergic pathology. Longitudinal study is necessary to determine whether increasing disease duration exacerbates the early cognitive deficits and affects new cognitive domains, in addition to producing increasing motor disability.

INTRODUCTION

Cognitive impairment is a common feature of idiopathic Parkinson's disease (PD). Although clinical dementia (e.g. according to DSM-III criteria) is recognized in only 10–15% of cases above that of an age-matched population (Brown and Marsden, 1984), subtle cognitive deficits are more common. Clinically non-demented patients may score outside the normal range on Mini Mental State examinations (Growdon and Corkin, 1987): furthermore, sensitive neuropsychological tests have shown specific cognitive

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impairments in patients who score normally on Mini Mental State tests and are not demented by clinical criteria (Sagar and Sullivan, 1988).

The principal knowledge of cognitive functions in PD is primarily derived from cross-sectional studies of pharmacologically treated patients. Cognitive dysfunction in PD has been observed in the domains of visuospatial capacity, memory and 'frontal lobe function'. Direct assessment of visuospatial capacity has shown deficits in PD even when no intellectual deficit is present and the tests include no motor component (Bowen *et al.*, 1972*b*, 1976; Boller *et al.*, 1984); however, some purported visuospatial deficits may be related more to set-shifting incapacity than to pure visuospatial function (Brown and Marsden, 1986). In memory capacity, PD patients show impaired verbal and non-verbal short-term recall (Bowen *et al.*, 1975; Taylor *et al.*, 1986*a*; Sullivan and Sagar, 1989, 1991) and recognition, and associative learning (Sahakian *et al.*, 1988) but relatively preserved long-term recognition (Flowers *et al.*, 1984; Sagar *et al.*, 1988*b*; Sullivan and Sagar, 1989). Long-term recall is mildly impaired and the capacity to date past events is disproportionately disrupted (Sagar *et al.*, 1988*a*). Procedural learning is also impaired (Heindel *et al.*, 1988; Saint-Cyr *et al.*, 1988) Frontal lobe functions, including set-shifting and set-formation (Bowen *et al.*, 1975; Cools *et al.*, 1984; Taylor *et al.*, 1986*a*; Downes *et al.*, 1989), temporal ordering (Sagar *et al.*, 1988*b*; Vriezen and Moscovitch, 1990), sequencing (Sullivan *et al.*, 1989) and planning (Morris *et al.*, 1988) are impaired in treated PD (reviewed in Sagar and Sullivan, 1988; Brown and Marsden, 1988*a*). Performance on these tasks varies across patients, however, with some early cases showing no impairment (Canavan *et al.*, 1989). Language processing and comprehension are, in general, preserved; defective performance on language tests may be due to impaired self-generation (Matison *et al.*, 1982) and motor dysfunction. Since these deficits have been found in chronically medicated patients, it is largely unknown whether the reported cognitive deficits are obligatorily linked to the pathology of the disease or are sequelae of pharmacological treatment.

The relationship between the motor and cognitive disorders of PD is controversial. Positive associations have been shown between severity of bradykinesia and visuospatial deficit, in contrast to tremor severity which paradoxically correlated with good spatial memory (Mortimer *et al.*, 1982). In a large longitudinal study, severity of cognitive deficits correlated with ageing and Hoehn and Yahr motor disability stage (Portin *et al.*, 1989). Presence of cognitive deficits was associated with hypokinesia and rigidity, rather than tremor. Analysis of more specific cognitive functions revealed that memory, hypokinesia and CSF HVA levels were correlated, whereas visuomotor function, hypokinesia and rigidity, but not HVA levels, were correlated. Although these observations provide tantalizing associations between different cognitive and motor processes, other laboratories have not confirmed these results (reviewed in Mortimer *et al.*, 1985). Positive associations between cognition and motor control have also been demonstrated in patients with 'on–off' motor swings; delayed verbal recall deteriorated during 'off' phases (Mohr *et al.*, 1989). By contrast, dissociation between frontal lobe capacity and motor disability occurred during withdrawal of levodopa treatment in chronically medicated patients (Gotham *et al.*, 1988). The improvement in cognition during withdrawal was attributed to removal of toxic effects of dopamine. The relationship between cognitive impairment and motor disability, removed from effects of medication, remains unclear.

The prevalence of depression in PD is nearly 50% according to some estimates (Mayeux *et al.*, 1981) and it occurs significantly more frequently than in the general population or in a population of people with other, severe debilitating diseases. Mesolimbic and mesocortical dopamine pathways may degenerate in PD, thus providing a neurological substrate for personality and mood changes (Agid *et al.*, 1984; Fibiger, 1984; Harvey, 1986), which may be pathophysiologically linked to some cognitive deficits (Cummings and Benson, 1984; Rogers *et al.*, 1987). However, the relationship between depression, motor control and cognition has not been fully explored.

In PD, several different pathological processes may contribute to changes in cognition and affect: dopamine deficiency, noradrenergic, cholinergic and serotonergic deficits; coexistent Alzheimer's disease (AD); superimposition of PD and ageing; and cortical Lewy body disease. Some of the affected neural systems also serve motor control so that involvement of these systems in cognition would predict a positive association between motor deficits and the appropriate processes of cognition and affect. First, a role for the basal ganglia in cognition has been proposed (Teuber, 1976; Marsden, 1982) which may be based on disruption to fronto-striatal circuits (Taylor *et al.*, 1986*a*). Secondly, although the major pathology of PD occurs in subcortical structures, dopaminergic cortical-subcortical circuits between the basal ganglia and the frontal lobes are also affected (Alexander *et al.*, 1986). Thus, specific cognitive deficits in PD could also be due to interruption of dopaminergic subcortico-cortical circuits (Javoy-Agid and Agid, 1980; Sagar, 1985).

Non-dopaminergic neurochemical deficiencies also occur in PD and may contribute to pathological changes in mood and cognition but are less obviously involved in motor control. Involvement of these systems predicts dissociations between cognitive, affective and motor deficits. Thus, for example, reduced affect and arousal during 'off' phases does not correlate with motor disability and may be due to noradrenergic deficiency (Marsden and Jenner, 1981; Brown *et al.*, 1984); noradrenaline metabolite levels may correlate specifically with reaction time and vigilance (Stern *et al.*, 1984). Altered serotonergic metabolism may underlie depression in PD independently of motor disability (Mayeux *et al.*, 1984). Anticholinergic agents have shown particularly deleterious effects on memory in PD patients despite improvement in motor control (de Smet *et al.*, 1982; Dubois *et al.*, 1987).

Cortical histopathology may also affect cognition in PD. First, histological changes of AD are found in the brains of some patients with PD and cholinergic deficits also occur. Although the neuropsychological profile of PD cannot be due entirely to coincidental AD, florid clinical dementia may be based upon Alzheimer-type pathology. Secondly, Lewy bodies may be diffuse in distribution throughout the cortex (Gibb *et al.*, 1987; Lennox *et al.*, 1989). The dementia of PD may be particularly associated with onset in the elderly owing to a combination of subclinical AD pathology and cortical Lewy body disease (Quinn *et al.*, 1986).

In chronically treated patients, the contribution of the primary pathology to the pathogenesis of these deficits remains uncertain. The progression of PD itself is a critical factor potentially influencing cognitive status. Many other factors, such as coexistent depression and duration of treatment, also influence cognitive function non-specifically in chronically treated patients. Few studies have examined cognitive function in detail in PD patients who have never received medication but deficits have been shown on tasks sensitive to frontal lobe function, including set-shifting and verbal fluency, even in non-depressed patients (Lees and Smith, 1983; Downes *et al.*, 1989), simultaneous matching-to-sample and non-verbal associative learning (Sahakian *et al.*, 1988). Rogers *et al.* (1987) showed prolonged cognitive processing time in early PD. Portin and Rinne (1980, 1987) showed impairment on tests of verbal and performance IQ, visual and motor perception and memory, as well as tests sensitive to frontal lobe function in untreated PD. In summary, studies have highlighted potentially important clinical associations of dementia in PD but no study of specific cognitive function has taken simultaneous account of the confounding factors of age, depression, drug responsiveness and nature of drug treatment. No study has examined specific cognitive functions in PD under different, specific regimes. Although the role of dopamine deficiency or excess has been addressed (Gotham *et al.*, 1988), these results require confirmation in a prospective study of untreated cases, owing to the chronic effects of levodopa treatment on dopamine receptors (Marsden and Jenner, 1981). Moreover, the effects of dopamine on other cognitive functions has been scarcely explored at all. One way to address brain-behaviour relationships in PD is to examine cognitive function in the earliest stages of the disease, before the introduction of treatment, using tests known to be sensitive to focal brain lesions, to control for confounding factors and to monitor response to specific pharmacological agents. Accordingly, we have undertaken a study of cognition in newly diagnosed, never-treated PD which incorporates several key experimental conditions: (1) initial assessment of newly diagnosed, untreated patients; (2) inclusion of consecutive rather than selected cases; (3) quantitative tests of specific rather than general cognitive function; (4) specific measures of affect; (5) quantitative tests of motor capacity; and (6) assessment of cognition, motor and psychiatric status within one study. Surprisingly, no previous study of PD has incorporated all of these conditions. This paper reports the findings on untreated, *de novo* patients at their first assessment; a later report will address the effects of specific treatment of these patients.

METHODS

Subjects

Sixty newly diagnosed, PD patients who had never received antiparkinsonian medication were consecutively recruited from the neurology outpatient clinics of the Royal Hallamshire Hospital, Sheffield. A sample of 40 age- and sex-matched, healthy control subjects (HCS) was obtained from a variety of sources: spouses of PD patients, non-professional hospital staff and patients without hearing impairment from an ear-nose-throat clinic. Of the 40, 3 HCS who were tested were later excluded: 1 for newly discovered, long-term, excessive alcohol consumption; 1 for clinical dementia; and 1 for inability to carry out the tests. Patients were recruited on the basis of a diagnosis of idiopathic PD and having had no previous exposure to neuroleptic or dopaminergic medication. Exclusion criteria were head injury with loss of consciousness in excess of 1 h, history of thyroid disease or diabetes, electroconvulsive therapy, major psychiatric disorder, psychoactive medication other than minor tranquillizers and hypnotics, alcohol consumption in excess of 56 units per wk, or any other condition known to impair central function other than PD. All PD patients fulfilled the diagnostic criteria of the PD Society: akinesia plus rest tremor, rigidity or postural instability and absence of any other condition that may produce signs of parkinsonism. No patient had undergone any neurosurgical operation. Patients were not selected on the basis of any behavioural criteria. All subjects were self-declared as right-handed except 4 who were left-handed (all PD) and 4 ambidextrous (2PD, 2HCS).

PD patients did not differ from HCS with respect to their premorbid IQ ($t = 1.24$, $P = 0.22$) as measured by the National Adult Reading Test (NART; Nelson and O'Connell, 1978), their present verbal IQ ($t = 0.5$,

$P = 0.62$) from their performance on the Vocabulary subtest of the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955) or their years of education ($t = 0.037$, $P = 0.71$). Thus other deficits are not due to differences in premorbid or current intellectual level. No patient was demented according to DSM-III criteria of the American Psychiatric Association (1987) (Table 1).

The patients were all tested before treatment. The group as a whole showed a positive motor response to antiparkinsonian treatment as later assessed by clinical and experimental measures of motor control

TABLE 1 CHARACTERISTICS OF SUBJECT GROUPS (MEAN AND RANGE)

Group	*Sex M/F*	*Age*	*Years of education*	*Premorbid IQ*	*Duration of disease (mths)*	*Motor disability rating (KCRS)*	*Dementia rating (BDS)*	*Depression rating (BDI)*
HCS	20/17	59 6	10 05	109 67	–	–	1.4	6.6
		(40.2–76.1)	(8–16)	(96–123)			(0–6)	(0–14)
PD	31/29	59.8	9.93	107 56	15.75	22.7	3.4	10 4
		(37.3–77.6)	(9–17)	(88–124)	(3–48)	(4 5–70)	(0–13)	(0–32)
Parkinson subgroups based upon Blessed Dementia Scale scores								
BDS 1	17/22	58.5	10 26	110.47	16.40	22.6	1 5	8.9
		(37.3–77.6)	(9–17)	(93–124)	(4–36)	(4.5–70)	(0–3)	(0–23)
BDS 2	14/7	62.4	9.33	102 29	14.67	23.0	6.8	13 1
		(53 9–73.4)	(9–11)	(88–120)	(3–48)	(6–68)	(4–13)	(1–32)
Parkinson subgroups based upon Beck Depression Inventory scores								
BDI 1	20/20	60.1	9.83	107 41	13 88	18.6	3 2	7 0
		(37.3–77.6)	(9–17)	(88–121)	(3–36)	(4 5–53)	(0–13)	(0–13)
BDI 2	7/5	59 1	9.83	106.50	19.22	41 1	4.5	21 6
		(45.7–69.2)	(9–13)	(89–124)	(8–48)	(18–70)	(0–13)	(14–32)

BDS 1 = Blessed Dementia Scale score 0–3; BDS 2 = Blessed Dementia Scale score > 3; BDI 1 = Beck Depression Inventory score 0–13; BDI 2 = Beck Depression Inventory score > 13

Procedure

Patients and controls received the following neuropsychological tests over a period of 1 to 2 d with suitable rest periods. The tests were carried out in a preplanned order so as to minimize interference between tests.

Motor disability. A neurologist gave the Kings College Rating Scale (KCRS; Brown *et al.*, 1984), which is a quantitative measure of clinical motor disability, including akinesia, tremor, rigidity and paucity of movement. Higher scores indicate poorer performance.

Manual dexterity was measured under unimanual and bimanual conditions by the Fine Finger Movements Test (Corkin *et al.*, 1981). The task required the subjects to rotate a mounted spindle between the thumb and first finger as quickly as possible for 30 s; performance was scored as the number of rotations achieved in each of 3 10-s intervals. This mode of scoring was parallel to that used in the test of semantic fluency, described below.

Global measures of cognitive and affective status. Overall cognitive function was assessed using the Blessed Dementia Scale (memory and orientation section) (BDS; Blessed *et al.*, 1968). Depression was rated using the Beck Depression Inventory (BDI; Beck *et al.*, 1961). Premorbid IQ was estimated with the NART and current verbal IQ with the Vocabulary subtest of the WAIS.

Memory. The Wechsler Memory Scale (WMS) was administered according to published instructions (Wechsler and Stone, 1945). In addition, recall of the logical memory passages, paired associates and visual reproduction subtests was reassessed after a 1-h delay (Milner, 1958); subjects were informed in advance of the second recall session.

Non-verbal long-term memory was also evaluated by the Rey–Osterrieth (1944) and Taylor (1969) complex figures. Subjects were presented with 1 of the 2 figures and given up to 5 min in which to copy it as accurately as possible. Subjects were told that they would be asked to draw the figure again 1 h later from memory. The copied and the recalled drawings were each scored on a 36-point scale (Taylor, 1969).

In statistical analysis, all recall scores were corrected for ability to copy by dividing the recall score by the copy score.

Forgetting in short-term memory was examined with the Brown–Peterson distractor paradigm in which recall of consonant trigrams was assessed over various distraction-filled intervals (Brown, 1958; Peterson and Peterson, 1959). The procedure employed 0, 3, 6, 9, 15 and 30-s retention intervals with serial 3 subtractions forming the distraction element.

Language. Language functions were assessed with tests of expression (Reporter's Test; De Renzi and Ferrari, 1978), comprehension (Token Test; De Renzi and Faglione, 1978) and confrontation naming (shortened Boston Naming Test; Huff *et al.*, 1986). Semantic fluency (Newcombe, 1969) was evaluated by asking subjects to generate in 1-min periods as many different items as possible from each of the following categories: inanimate objects, animals and birds/colours in alternation For the objects and animals condition, performance over the first 30 s was measured as the number of words generated in each 10-s interval in order to determine change in performance with time; this mode of scoring was parallel to that used for motor speed in the Fine Finger Movements Test.

Executive function: frontal lobe tasks. Frontal lobe capacity was assessed using the Milner (128 cards; 1963) version of the Wisconsin Card-Sorting Test (WCST) and qualitative error scores of the Picture Arrangement subtest of the WAIS (McFie and Thompson, 1972). Performance on the WCST was scored according to the method of Heaton (1981) to yield 10 measures. The Picture Arrangement subtest of the WAIS was administered in the standard way, with time limits, but subjects were permitted to continue beyond the time limit. Separate scores were obtained from the timed and untimed conditions in order to control for pure motor influences on performance. Qualitative error scores (McFie errors) were calculated for each incorrect trial (McFie and Thompson, 1972).

Cognitive sequencing and working memory were assessed with a test of digit ordering (modified from Corkin, 1968). In this task subjects were read a random selection of 7 digits (e.g 5–3–6–2–7–2–1) and were required to reorder the items by memory and repeat them in ascending fashion (in this example, 1–2–2–3–5–6–7). Each subject was given 15 trials. For each trial, 1 point was awarded for each digit placed in its correct position until a response broke the ascending sequence (e.g. 6 followed by 4). Maximum score was 7 per trial (total 105); if a subject reported more than 7 digits, only the first 7 were scored. Responses that did not come from the test presentation but, nevertheless, maintained ascending sequence were tolerated but not scored.

Visual perception. In the Gollin Incomplete Pictures Test, subjects viewed partially degraded line drawings of 10 items for about 1 s each and were required to identify each item (Gollin, 1960). The test consisted of 5 trials of 10 items. The 10 items were initially presented in their most degraded form; on subsequent trials, integrity was gradually increased. The score was the total number of errors across all 50 presentations. Without warning, subjects were required to recall the test items after a 1-h delay and the perceptual test was then repeated in an identical fashion to that given 1 h earlier.

Constructional praxis. Drawing ability was assessed by asking subjects to copy the Rey–Osterrieth figure. The Matchsticks Test (Butters and Barton, 1970) comprised 2 conditions. In the first, the examiner displayed a series of 5 patterns using flat wooden sticks painted to look like matchsticks and the subject was required to copy each pattern using similar wooden sticks (copy condition). In the second, the examiner displayed 5 additional patterns and the subject was required to copy them in a form rotated through 180 degrees (rotation condition).

Statistical analysis

Differences between data sets were evaluated by one-way and repeated measures analyses of variance (ANOVA) Planned comparisons between sets of data were made using *t*-tests for 2 independent samples (two-tailed, unless otherwise stated). Correlations were determined with Pearson Product-Moment Correlation Coefficient r.

RESULTS

Compared with the HC group, the PD group showed significantly inferior performance on 10 of the 15 cognitive tests. In no instance was the performance of the PD group significantly better than that of the HC group. The deficits were not obviously related to fatigue because they occurred on tests given early as well as late in the test battery.

Motor control

Fine Finger Movements Test. PD patients differed significantly from HCS on all 4 measures of this test. They rotated the spindle more slowly, under both unimanual and bimanual conditions: left hand unimanually ($t = 8.56$, $P < 0.001$), right hand unimanually ($t = 8.27$, $P < 0.001$), left hand bimanually ($t = 7.79$, $P < 0.001$) and right hand bimanually ($t = 9.30$, $P < 0.001$).

Change in performance over the 3 10-s intervals of each test was evluated by repeated measures ANOVA of Group × Interval for each condition separately. For each condition, there was a main effect of Group ($P < 0.0001$) and Interval ($P < 0.0001$); the Group × Interval interaction was significant for the right bimanual condition ($F = 3.40$, $P < 0.05$) (Fig. 1) and borderline significant for the left bimanual ($F = 2.75$, $P = 0.07$) and left unimanual conditions ($F = 3.03$, $P = 0.05$); the interaction on the right unimanual condition was clearly not significant ($F = 1.59$, $P = 0.21$). Inspection of the results

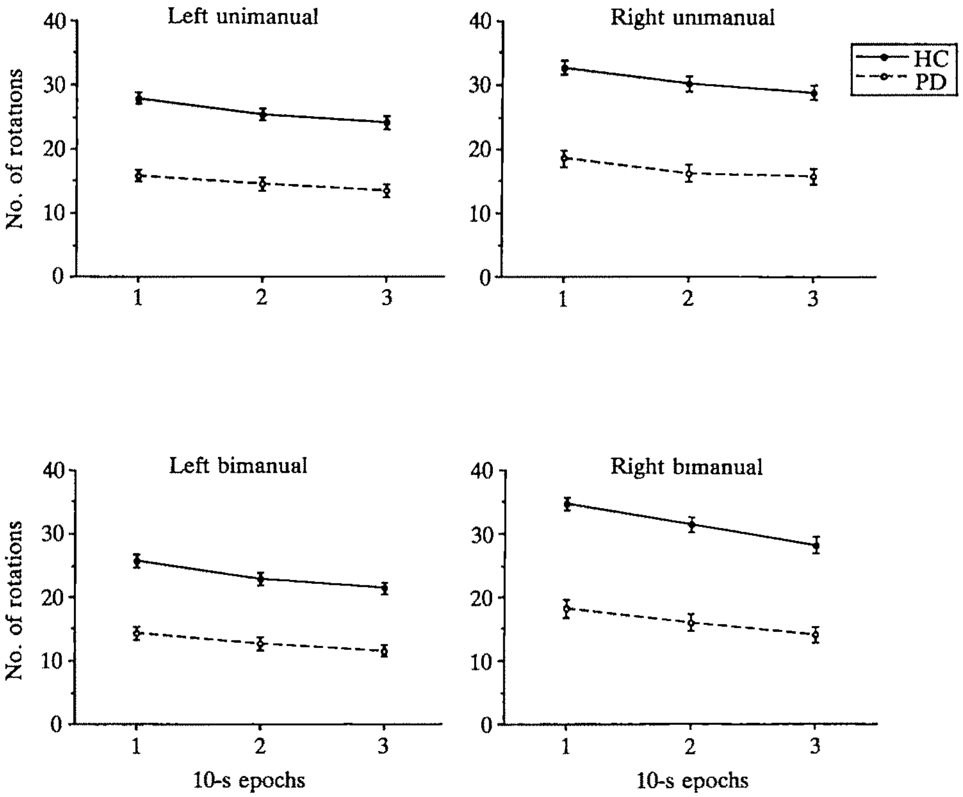

FIG. 1. Mean number of rotations per 10-s epoch for each of the 4 conditions of the Fine Finger Movements Test (left and right unimanual, left and right bimanual); vertical bars signify standard error of the mean. PD patients rotated the spindle more slowly in all conditions, particularly over the first 10 s.

shows that the interactions are slight and not clearly meaningful (Fig. 1). PD patients performed considerably more slowly than did HCS at all intervals for all conditions ($P < 0.0001$).

Memory

Wechsler Memory Scale. PD patients differed from HCS in overall MQ ($t = 3.99$, $P < 0.001$) despite normal estimated IQ (Fig. 2). Analysis of the subtests showed that PD patients were impaired in Mental Control ($t = 2.22$, $P < 0.05$), Logical Memory ($t = 3.73$, $P < 0.001$), Digit Span ($t = 2.03$, $P < 0.05$), Visual Reproduction ($t = 2.37$, $P < 0.05$) and Associate Learning ($t = 2.79$, $P < 0.01$). When the Digit Span subtest was broken down into its forward and backward components, PD patients differed significantly from HCS only on the backwards measure (forwards, $t = 0.70$, $P = 0.49$; backwards, $t = 2.5$, $P < 0.02$) (*see* Table 2).

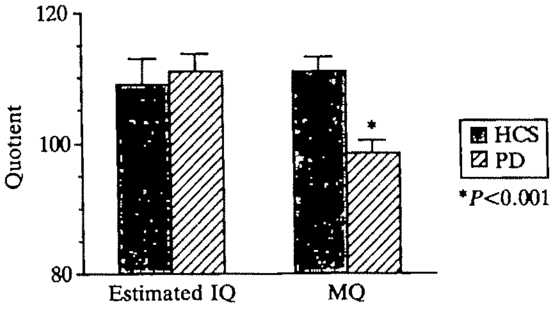

FIG. 2. Mean IQ, as estimated from the WAIS Vocabulary scaled scores multiplied by 10, and the Wechsler Memory Quotient (MQ); vertical bars signify standard error of the mean. The PD group was impaired in MQ despite normal estimated IQ.

Separate analyses considered immediate and 1-h delayed recall of verbal and non-verbal material separately (Table 2). For Logical Memory, two-way ANOVA of Group by Condition (immediate vs delayed recall) showed main effects of Group (F = 12.5, $P < 0.001$) and Condition (F = 288.24, $P < 0.001$). Paired comparisons showed that PD patients were impaired in immediate ($t = 3.73$, $P < 0.001$) and delayed recall ($t = 2.59$, $P < 0.02$). In addition, a significant Group by Condition interaction (F = 4.86, $P < 0.05$) reflected relatively greater impairment in the PD group for the immediate condition. For Associate Learning, three-way ANOVA of Group by Condition (immediate recall of trial 3 vs delayed recall) by Difficulty (easy, hard pairs) showed main effects of Group (F = 8.16, $P < 0.01$). Condition (F = 34.51, $P < 0.001$) and Difficulty (F = 932.36, $P < 0.001$) but no significant interactions. PD patients were impaired under immediate and delayed conditions for both levels of difficulty.

The PD group was impaired in copy of the items of the Visual Reproduction subtest ($t = 3.19$, $P < 0.01$). Therefore, analysis of non-verbal memory was carried out using the copy performance as a covariate in a two-way ANOVA of Group by Condition (immediate vs delayed recall). There was a main effect of Condition (F = 64.73, $P < 0.001$) but not Group (F < 1); delayed recall was more difficult for both groups. The interaction was not significant. Thus, the poor scores on the Visual Reproduction subtest cannot be attributed to memory deficits.

TABLE 2 SCORES ON THE SUBTESTS OF THE WECHSLER MEMORY SCALE

Subtest	*HCS*	*PD*	*P*
Information	5.2	5.2	
	(0.11)	(0.10)	
Orientation	5.0	4.9	
	(0.04)	(0.03)	
Control	7.1	6.2	< 0.05
	(0.26)	(0.32)	
Logical memory			
Immediate	7.9	5.7	< 0.01
	(0.50)	(0.32)	
Delay	4.3	2.9	< 0.01
	(0.45)	(0.30)	
Delay: immediate	0.53	0.48	
	(0.03)	(0.04)	
Digits	11.9	11.1	< 0.05
	(0.33)	(0.22)	
Associate learning	13.1	11.2	< 0.01
	(0.55)	(0.42)	
Visual reproduction			
Copy	11.6	10.2	< 0.01
	(0.27)	(0.34)	
Immediate copy	0.66	0.58	
	(0.04)	(0.04)	
Delay copy	0.50	0.45	
	(0.04)	(0.04)	

Figures indicate mean values and (standard errors). *P* refers to significant differences between groups

Rey–Osterrieth and Taylor complex figures. The pattern of deficit on the Visual Reproduction subtests of the WMS was mirrored in copy and recall of the complex figures. Compared with HCS (mean 28.7, SEM 0.85), the PD group was impaired in copy of the figure (mean 25.1, SE 1.11; $t = 2.53$, $P < 0.02$) but not in delayed recall when copy performance was used as a covariate (delayed recall scores: for HCS, mean 12.9, SEM 1.11; for PD, mean 11.3, SEM 1.41; one-way ANOVA, $F = 1.10$).

Brown–Peterson Distractor Test. A two-way ANOVA of Group (PD, HCS) × delay (0, 3, 6, 9, 15, 30 s) gave main effects for group ($F = 9.31$, $P < 0.005$) and delay ($F = 149.5$, $P < 0.001$) but no interaction. Pairwise comparisons showed that the PD group performed significantly more poorly than the HC group at every delay except at 0 s (Fig. 3). The normal performance of the PD patients at the 0-s condition indicates that they could adequately perform the test.

Tests of frontal lobe function

Wisconsin Card-Sorting Test. The PD group sorted significantly more cards before achieving the first category ($t = 2.61$, $P < 0.02$). In addition, the PD group showed a trend to more errors ($t = 1.56$, $P = 0.06$, one-tailed), particularly the perseverative type ($t = 1.77$, $P < 0.05$, one-tailed) and perseverative responses ($t = 1.49$, $P = 0.07$, one-tailed). The groups did not differ in number of categories achieved, correct responses,

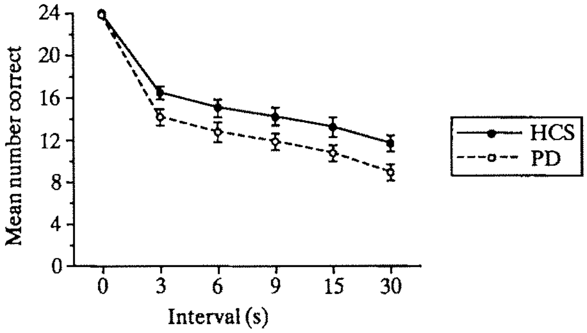

Fig 3 Mean scores at the 6 retention intervals of the Brown–Peterson Distractor Test of short-term memory, vertical bars signify standard error of the mean. The PD group showed similar impairment at all intervals except 0 s

TABLE 3 RESULTS OF THE WISCONSIN CARD-SORTING TEST

	HCS	*PD*	*P*
Categories achieved	4.19 (0.39)	3.55 (0.35)	
Correct responses	34.9 (1.90)	35.4 (1.81)	
Total errors made	51.2 (2.72)	57.0 (2.51)	
Unique responses	4.11 (1.15)	3.60 (0.60)	
Perseverative errors (%)	22.1 (1.64)	26.2 (1.69)	
Perseverative responses (%)	33.5 (2.51)	39.0 (2.73)	
Failure to maintain set	1.03 (0.14)	1.10 (0.18)	
Conceptual level response (%)	45.4 (2.76)	40.5 (2.52)	
Learning to learn	−4.01 (1.75)	−2.36 (1.74)	
Cards to 1st category	16.2 (1.34)	26.0 (3.48)	< 0.05

Figures indicate mean values and (standard errors) *P* refers to significant differences between groups.

unique errors, conceptual-level responses, learning-to-learn or failure to maintain set (Table 3).

Digit ordering. PD patients were significantly impaired in their ability to order the digits ($t = 4.75$, $P < 0.001$). This impairment contrasts with their normal forward digit span (Fig. 4).

Picture arrangement. Compared with the HC group, the PD group performed significantly more poorly on this subtest of the WAIS ($t = 2.20$, $P < 0.05$) and made more McFie errors ($t = 3.05$, $P < 0.005$). The poor performance is unlikely to be due to motor disability alone since the difference persisted in the untimed condition

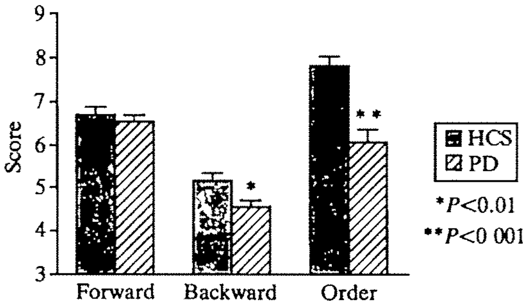

FIG. 4. Mean forward and backward digit span, and scores on the Digit Ordering Test. (Digit ordering scores divided by 10 for ease of display.) Backward digit span and digit ordering, which involve reordering items in memory, were impaired in the PD group, despite normal immediate memory, as measured by forward digit span.

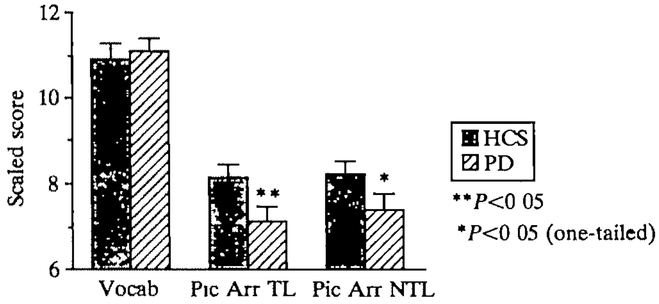

FIG 5. Mean Vocabulary and Picture Arrangement scaled scores (timed and untimed); vertical bars signify standard error of the mean. The PD group was impaired in Picture Arrangement, whether or not time was taken into account, but not in Vocabulary.

($t = 1.71$, $P < 0.05$, one-tailed). The poor performance of the PD patients on this subtest contrasts with their normal scores on Vocabulary (Fig. 5).

Language (Tables 4, 5 and 6)

Boston Naming Test. A pairwise comparison showed no group differences on this test. PD patients were equally able to name the line drawings without cues as were HCS ($t = 0.42$, $P = 0.67$).

Token Test. Language comprehension, as measured by this task, was unimpaired in PD ($t = 1.44$, $P = 0.154$).

Reporter's Test. In contrast to language comprehension, language expression was impaired in the PD group ($t = 2.14$, $P < 0.05$).

Semantic fluency. Compared with the HC group, the PD group generated fewer words from the semantic category of objects ($t = 1.94$, $P < 0.05$, one-tailed), but not animals ($t = 1.11$, $P = 0.14$, one-tailed). The patient group also showed impaired fluency in the alternating birds/colours condition ($t = 1.77$, $P < 0.05$, one-tailed) (Table 4).

In order to compare with the Fine Finger Movements Test, change in performance over the first 3 10-s intervals of each fluency condition (objects and animals) was evaluated by repeated measures ANOVA of Group × Interval for each condition separately. For objects, there was a main effect of Group ($F = 4.22$, $P < 0.05$) and Interval ($F = 120$, $P < 0.0001$); the Group × Interval interaction was not significant ($F < 1$). For animals,

TABLE 4 SEMANTIC FLUENCY FOR 3 CONDITIONS MEAN (AND STANDARD ERROR)

Group	Objects	Animals	Birds/Colour
HCS	27.2 (1.3)	19.6 (0.6)	15.8 (0.6)
PD	24.1* (1.0)	18.6 (0.6)	14.7* (0.5)

*$P < 0.05$, one-tailed.

there was a main effect of Interval (F = 498, $P < 0.0001$) but not Group (F < 1). The Group × Interval interaction was not significant (F = 1.5, $P = 0.23$). In both conditions, output of both groups was greatest in the first 10 s and declined over the second and third 10-s periods (Fig. 6).

Visuospatial function

Gollin Incomplete Pictures Test. The number of trials taken by PD patients to recognize partially degraded line drawings did not differ from that of HCS ($t = 1.08$, $P = 0.29$). By contrast, delayed recognition of these same items was mildly impaired ($t = 1.81$, $P < 0.05$, one-tailed), despite unimpaired, delayed free recall of the picture names ($t = 0.97$, $P = 0.33$).

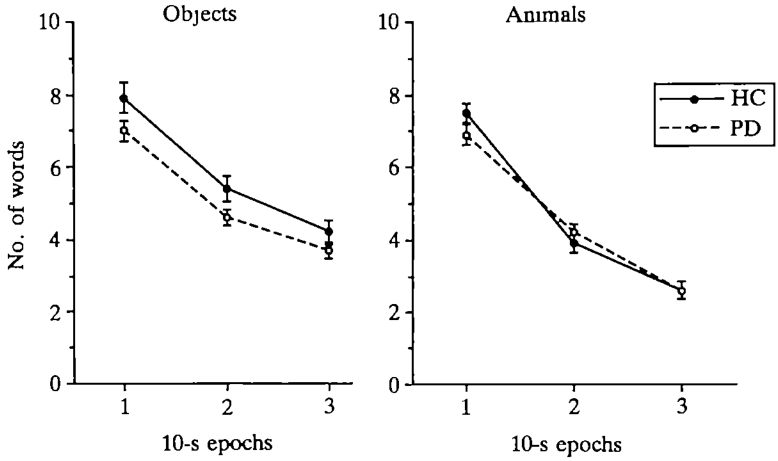

FIG. 6 Mean number of words generated per 10-s epoch in the objects and animals conditions of the semantic fluency test; vertical bars signify standard error of the mean. The output of the PD group was significantly lower than that of the HC group during all 3 epochs of the objects condition.

The pattern of performance across trials was analysed using a three-way ANOVA of Group by Condition (immediate, delayed) by Trial (levels 1–5 of stimulus degradation). The analysis showed main effects of Condition (F = 438.75, $P < 0.001$) and Trial (F = 515.08, $P < 0.001$) with a significant Condition by Trial interaction

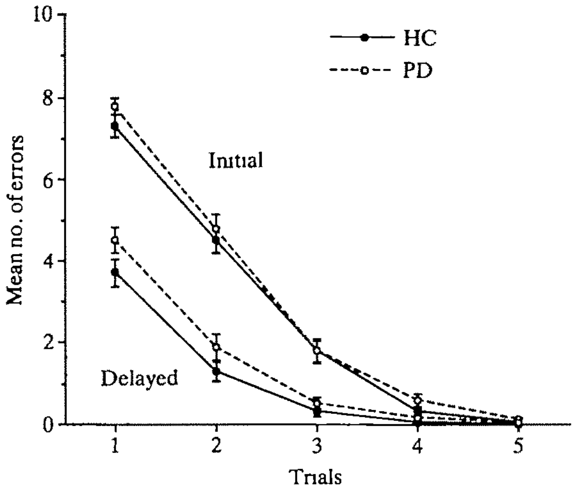

FIG 7 Scores on the initial test and 1-h retest of the Gollin Incomplete Pictures Test (means and standard errors). The PD group performed normally across all trials of both sessions, except Trial 1 of the retest

(F = 112.16, $P < 0.001$); the main effect of Group and the remaining interactions were not significant. Inspection of the results (Fig. 7) shows that the minor impairment in delayed recognition is attributable largely to their performance on the first trial of the delayed condition.

Matchsticks Test. Repeated measures ANOVA of Group×Condition (copy, rotation) showed a main effect of Condition (F = 48.6, $P < 0.0001$) but no effect of Group and no Group×Condition interaction. Both groups made more errors in the rotated condition than the copy condition but the PD group was not impaired on either measure [errors mean (SD): for copy, HCS 1.27 (1.50), PD 0.73 (1.31); for rotation, HCS 2.32 (1.62), PD 2.2 (1.69)].

Analysis according to Blessed Dementia Scale (BDS) scores (Table 5)

For this analysis, PD patients who scored above 3 on the BDS were treated as cognitively impaired. This cut-off point was chosen on the grounds that a score of 4 was more than 2 standard deviations from the mean score of the HC group. Those patients who scored abnormally on the BDS differed significantly in every cognitive test area from HCS and also from those PD patients scoring normally on the BDS (Table 5). The patients scoring normally, however, continued to show cognitive deficits. Thus this PD subgroup differed from the HC group in overall MQ (t = 1.82, $P < 0.05$, one-tailed), the Logical Memory subtest of that scale (t = 2.05; $P < 0.05$), the short-term memory distraction task (Brown–Peterson paradigm) (t = 2.58, $P < 0.05$) and the Digit Ordering Test (t = 2.58, $P < 0.02$).

In order to examine the effect of cognitive impairment on timed semantic fluency and Fine Finger Movements Test, the performance on each of these tests in 10-s epochs was analysed by two-way ANOVA across the 2 PD subgroups. For the objects and animals categories of the fluency test, PD patients who performed abnormally on the

TABLE 5 RELATIONSHIP OF COGNITIVE TEST RESULTS TO BDS SCORE

	HCS	*P*	*BDS 1*	*P*	*BDS 2*
Memory					
WMS					
MQ	110	< 0.05	105	< 0.01	86
Logical memory	7.9	< 0.05	6.6	< 0.01	4.0
Associate learning	13.1		12.4	< 0.01	8.9
Brown–Peterson	95.4	< 0.05	87.1	< 0.01	72.1
Language					
Token Test	33.8		33.6	< 0.05	32.2
Reporter's Test	23.2		22.8	< 0.01	20.5
Naming	35.1		35.6	< 0.05	33.3
Fluency					
Objects	27.2		26.5	< 0.01	19.8
Animals	19.6		19.4	< 0.05	17.0
Birds/colours	17.5		16.9	< 0.05	14.8
Frontal					
WCST					
Categories	4.2		4.1	< 0.01	2.5
Errors	51.2		52.6	< 0.01	65.1
Cards to 1st category	16.2		24.5		28.7
Digit ordering	78.1	< 0.01	67.9	< 0.01	47.6
Picture arrangement					
No time limit	8.2		8.1	< 0.01	6.2
Time limit	8.2		7.4	< 0.05	5.9
McFie errors	1.2		1.8	< 0.01	3.6

Figures indicate mean values. *P* refers to significant differences between the subject groups on either side

BDS produced significantly fewer words than did the PD patients who performed normally on the BDS (objects: $F = 19.0$, $P < 0.0001$; animals: $F = 9.49$, $P < 0.01$); both subgroups showed an Interval effect, with the greatest number of words produced in the first 10 s (objects: $F = 75.2$, $P < 0.0001$; animals: $F = 75.2$, $P < 0.0001$), but no interaction (objects: $F < 1$; animals: $F = 1.15$). All 4 conditions of the Fine Finger Movements Test showed the same pattern: both subgroups made fewer spindle rotations as the test progressed ($P < 0.0001$ in all cases), but no group differences or interactions were present ($F < 1$ in all cases).

Analysis according to Beck Depression Inventory (BDI) scores (Table 6)

For this analysis, a score of 14 and above on the BDI was used to indicate the subgroup of PD patients deemed depressed, though it should be noted that no patient had clinically significant depression requiring antidepressant drugs. The subgroup of patients with high BDI scores made more McFie errors on the Picture Arrangement subtest than did those with low BDI scores ($t = 2.41$, $P < 0.02$). The subgroups did not differ significantly on any other cognitive measure (Table 6).

The non-depressed subgroup, however, continued to show differences from the HC group that were similar to those found in the PD group as a whole. The deficits were again most noticeable with respect to memory tasks. They showed deficits on MQ

TABLE 6 RELATIONSHIP OF COGNITIVE TEST RESULTS TO DEPRESSION SCORE

	HCS	*P*	*BDI 1*	*P*	*BDI 2*
Memory					
WMS					
MQ	110	< 0.01	99		93
Logical memory	7.9	< 0.01	5.6		5.4
Associative learning	13.1	< 0.01	11.2		11.2
Brown–Peterson	95.4	< 0.01	81.6		85.9
Language					
Token Test	33.8		33.4		33
Reporter's Test	23.2		22.4		21.6
Naming	35.1		34.7		33.5
Fluency					
Objects	27.2	< 0.05	24.2		22.3
Animals	19.6		18.4		18.3
Birds/colours	17.5	< 0.05	16.2		16.2
Frontal					
WCST					
Categories	4.2		3.8		2.6
Errors	51.2		55.8		61.3
Cards to 1st category	16.2	< 0.05	26.5		24.0
Digit ordering	78.1	< 0.01	61.3		56.7
Picture arrangement					
No time limit	8.2		7.7		6.5
Time limit	8.2		7.2		6.3
McFie errors	1.2		2.0	< 0.05	3.8

Figures indicate mean values. *P* refers to significant differences between the subject groups on either side

($t = 3.49$, $P < 0.001$), Logical Memory ($t = 3.84$, $P < 0.002$) Associate Learning ($t = 2.70$, $P < 0.01$) and the Brown–Peterson task ($t = 2.64$, $P < 0.02$). Some frontal measures also differed between non-depressed patients and HCS: score on the digit ordering task ($t = 4.00$, $P < 0.001$) and the number of cards to first category on the Wisconsin Card-Sorting Test ($t = 2.26$, $P < 0.05$). Slight differences between the non-depressed PD subgroup and HC group were found for 2 of the verbal fluency measures: inanimate objects ($t = 1.85$, $P < 0.05$, one-tailed) and birds/colours ($t = 1.68$, $P < 0.05$).

When performance of the depressed PD subgroup was compared with that of the HC group, the pattern of impairment was similar to that of the PD group as a whole but more severe. In addition, and in contrast to the non-depressed patients, the depressed patients showed a significant deficit on the Wisconsin Card-Sorting Test (categories, $P < 0.05$; errors, $P = 0.09$) and on Picture Arrangement scaled scores ($t = 2.01$, $P < 0.05$) (Table 6).

In contrast to the similar performance of the 2 PD subgroups on the cognitive tests, the depressed patients had greater clinical motor disability, as shown by a higher score on the KCRS, than did the non-depressed patients ($t = 4.63$, $P < 0.0001$). Fine Finger Movements scores, however, did not differ significantly between the subgroups in any condition.

The depressed and non-depressed patients did not differ from each other in the pattern of performance across the first 3 10-s intervals of the category fluency or Fine Finger Movements Tests, except for the right bimanual condition in which the depressed subgroup made fewer rotations overall than did the non-depressed subgroup ($F = 4.52$, $P < 0.05$).

Relationship among cognition, affect and motor control

The relationship between measures of motor control, affect and cognition were evaluated by a series of Pearson correlation coefficients, r (Table 7). Scores from the 2 tests of motor control, KCRS and Fine Finger Movements, were highly correlated ($P < 0.005$). Motor disability was also consistently associated with severity of depression as measured by the BDI score (for KCRS, $P < 0.001$; for Fine Finger Movements, $P < 0.025$). By contrast, correlations between motor disability and cognition were, in general, weak, non-significant and inconsistent.

KCRS score showed no significant correlation with performance on any of the tests of memory, executive function, language or visuospatial capacity except for copy of the Visual Reproduction figures ($P < 0.001$) which also depends on motor control.

Fine Finger Movement score (mean of the left and right unimanual scores) showed no significant correlation with the memory tests except for backwards block span, delayed recall of the Rey figure and immediate and delayed recall of the WMS drawings which also involve motor control. Among the executive tests, the correlations were insignificant except for weak correlations with Picture Arrangement scores ($r = 0.26$; $P < 0.05$), which contrasts with the lack of correlation with KCRS score ($r = -0.11, -0.12$). Among the visuospatial tests, a strong correlation was found with the copy of the WMS drawings, which involves motor control ($P = 0.006$), and is consistent with the correlation with KCRS score. A weak correlation was also found with the score on the Gollin retest ($r = -0.32$; $P < 0.05$) which contrasts with the lack of correlation with KCRS score ($r = 0.11$). No significant correlation was found with any of the measures of language. The weak correlations, that were inconsistent across the 2 motor tests, are regarded as possibly spurious in light of the large number of correlations performed.

DISCUSSION

The results from this study show that patients with PD but no clinical dementia have significant cognitive impairment in the earliest stages of the disease and before treatment. Indeed, the abnormalities were present at a disease duration of as little as 16 mths. The deficits included immediate recall of verbal material; set formation, cognitive sequencing and working memory; language expression and semantic fluency. Motor disability was especially poor in the depressed patients, but cognition did not relate substantially to measures of motor disability. Set-formation and set-shifting showed some relationship to depression, but otherwise there was no association between cognition and depression. The deficits were detectable even in patients who scored normally on a Mini Mental State examination. The patients were direct referrals from the community to general neurology outpatient clinics and were not selected by any predetermined criterion other than those appropriate for diagnosis. Thus, the patient population is probably a

TABLE 7 RELATIONSHIP OF MOTOR CONTROL TO COGNITION AND AFFECT CORRELATION COEFFICIENTS

Test	*KCRS*	*P*	*Fine Finger Movements*	*P*
Motor control				
Fine Finger Movements				
Left unimanual	−0.45	< 0.005		
Right unimanual	−0.40	< 0.005		
Left bimanual	−0.47	< 0.005		
Right bimanual	−0.47	< 0.005		
Memory				
MQ	0.03		0.10	
Logical memory	0.16		0.02	
C score	0.16		0.02	
Visual reproduction	−0.25		0.30	< 0.025
D score	−0.24		0.32	< 0.025
Forward digit span	−0.01		0.13	
Backward digit span	−0.14		0.23	
Forward block span	−0.05		0.12	
Backward block span	−0.09		0.32	< 0.02
Brown−Peterson	−0.06		0.25	
Rey figure delayed recall	−0.26		0.37	< 0.025
Gollin Incomplete Pictures: item recall	−0.05		0.27	
Executive function				
Wisconsin Card-Sorting				
Categories	0.04		−0.03	
Errors	−0.01		−0.09	
Picture arrangement				
Timed	−0.11		0.26	< 0.05
Untimed	−0.12		0.26	< 0.05
McFie score	0.17		−0.18	
Digit ordering	−0.11		0.15	
Visuospatial				
Matchsticks				
Copy	0.10		−0.23	
Rotated	0.16		−0.17	
Gollin Incomplete Pictures				
Immediate	0.13		−0.27	
Delayed	0.11		−0.32	< 0.05
Copy of WMS drawings	−0.44	< 0.001	0.35	< 0.01
Rey figure: copy	−0.29		0.20	
Language				
Vocabulary	−0.07		0.02	
Token	0.09		0.08	
Reporter's	0.06		0.14	
Confrontation naming	0.08		0.25	
Category fluency				
Objects	−0.15		0.03	
Animals	−0.17		0.16	
Birds/colours	−0.07		0.01	
Affect				
Beck Depression Inventory	0.46	< 0.001	−0.33	< 0.025

representative sample of PD. The theoretical implications of the findings are discussed below.

Memory

Overall MQ differed by almost 1 standard deviation from the scores of normal subjects and from an estimate of the patients' own premorbid IQ as measured by the NART. In so far as Vocabulary provides an estimate of current Verbal IQ (at least in normal subjects; Wechsler, 1955), the impairment in memory also occurred despite normal, current IQ. Of course, any IQ measure may be inappropriate for the evaluation of cognitive decline in dementia. However, this pattern is commensurate with clinical observations of subcortical dementias (Albert *et al.*, 1974; Cummings and Benson, 1984). As expected, these findings were more pronounced for those patients who scored abnormally on a Mini Mental State examination. The fact that PD patients displaying normal BDS scores were impaired on a number of memory measures reinforces the notion that Mini Mental State examinations are insensitive in detecting early memory impairment in neurodegenerative diseases (Sagar and Sullivan, 1988).

Deficits were, however, by no means found on every memory task. This result shows, first, that no single test is in itself adequate to detect memory impairment and, secondly, that the pattern of impairment indicates selective deficits in component processes of memory. In particular, PD patients were impaired in immediate recall of the material from Logical Memory and Associate Learning but recalled, after a 1-h delay, at least as much of their immediate response as did normals; that is, the information recalled initially was no more vulnerable to decay in the PD patients than in the HC subjects. Furthermore, the results of the Brown – Peterson distraction task highlighted differences between the groups but no differential impairment related to retention interval. PD patients forgot more of the trigrams than normals but not in a way that would suggest a more rapid decay of stored information. Beyond a 3-s retention period, forgetting curves did not differ in their gradient. This pattern of results suggests that the poor performance of the PD group after the 0-s retention interval on the Brown – Peterson Test is likely to be related more to impairment in the immediate registration of information than to accelerated rate of forgetting (unless the forgetting is limited to the first 3 s). Theoretically, motor deficits of speech could produce selective disadvantage in distraction or recall for the PD group either by diverting attentional resources or delaying verbal output. Diversion of attentional resources would predict greater deficits with longer periods of distraction; a constant deficit in speech initiation would predict the greatest effect at the short intervals. However, neither hypothesis is supported because the deficit was constant across all distraction-filled intervals. Thus, the memory deficit in PD is more likely to be associated with the breakdown of processes of registration or retrieval of information during the early retention phase of short-term memory.

Observations of a deficit in immediate recall or recognition are compatible with results of other studies of memory performance in PD. Deficits occur in the immediate but not delayed recall of prose passages and geometric figures (Bowen *et al.*, 1972*a*; Taylor *et al.*, 1986*a*; Sullivan *et al.*, 1989; Sullivan and Sagar 1991). A similar pattern of performance has been shown on verbal and non-verbal recognition tasks; in contrast to AD patients, PD patients showed impaired performance under short-term but not long-term conditions (Sagar *et al.*, 1988*b*; Sahakian *et al.*, 1988; Sullivan and Sagar, 1989). The delay in producing correct responses may underlie the clinical phenomenon of bradyphrenia, even though the underlying deficits do not necessarily involve slowing of cognitive processes.

Results of memory performance after a delay in PD are inconsistent. In some studies (e.g. Levin *et al.*, 1989), long-term recall remains impaired although the *proportionate* decline relative to immediate recall is no greater than that of normal subjects. In other studies (e.g. Taylor *et al.*, 1986*a*; Warrior *et al.*, 1990; Sullivan and Sagar, 1991), however, long-term memory in PD patients is preserved *relative* to their own short-term memory scores and indeed may not differ significantly from the long-term memory performance of normal subjects. In the present study, performance of the PD patients on Associate Learning and the Brown–Peterson Test was equivalently impaired under short- and long-term conditions; on Logical Memory, the group showed relative preservation of long-term memory.

These conflicting observations have different implications for the effects of PD pathology on cognitive processes. Equivalent, but impaired performance under short- and long-term conditions is compatible with deficits in processes affecting the registration of information (such as attention or encoding) or retrieval. Normal long-term, but impaired short-term, memory implies adequate registration and suggests deficits in the speed, but not accuracy, of registration, or, in a parallel processing model, selective disruption of short-term memory or a hierarchical attentional process (Sagar *et al.*, 1988*b*; Sullivan and Sagar, 1991). In an information-processing model, it is possible that registration processes may be inefficient, yet function at a level adequate to allow sufficient encoding to achieve normal long-term memory performance, particularly on recognition. Although inefficient registration may be associated with a faster rate of forgetting, normal performance after a delay could result if some items were encoded normally, and therefore retained, whilst other items were poorly encoded and lost to recall. Clearly, more than one deficit may exist to produce this pattern of results. However, the best single hypothesis of these paradoxical observations is an abnormality related to the registration of information, due to limited attentional processes, or encoding or retrieval from short-term memory. The single origin of this impairment may be a reduction in the efficiency of working memory.

Language function

Language function was largely unimpaired in this group of early, untreated PD patients, a finding compatible with the initial description of 'subcortical dementia' (Albert *et al.*, 1974). Comprehension and confrontation naming were entirely normal. Although mild deficits were present on the Reporter's Test and on tests of semantic fluency, as previous studies have shown (reviewed in Brown and Marsden, 1988*a*) the underlying processes may be more related to self-generated activity than to language functions *per se*. For example, PD patients also show greater impairment on recall than recognition, on response to internal as opposed to external cues (Brown and Marsden, 1988*b*) and on the self-ordering task of Petrides and Milner (1982) (Gotham *et al.*, 1988).

PD patients may show a deficit for objects and alternating birds/colours, but not animals, because of the different nature of the search strategies involved for each category: objects is a less well-defined category than animals and has a greater search field; the birds/colours condition demands explicit attentional shifting. Gotham *et al.* (1988) also found disproportionate deficits in alternating fluency compared with single category fluency in chronic PD patients. Thus, our findings are compatible with a deficit in an hierarchical control system involved in shifting attention between cognitive processes, especially when motivated by internal cues (Brown and Marsden, 1988*b*; Morris *et al.*, 1988; Sagar *et al.*, 1988*b*).

Visuospatial capacity

Visual perceptual deficits have been frequently cited as one of the more prominent cognitive deficits of PD (e.g. Bowen *et al.*, 1972*b*, 1976; Boller *et al.*, 1984), but more recently, the impairment has been redefined in terms of other cognitive deficits that are more persistently found in the disorder. According to Brown and Marsden (1986), deficits have been found on visuospatial tasks only when set-shifting is also involved. Our PD patients performed normally in recognition of degraded line drawings (Gollin Test) which does not involve a major set-shifting component. Moreover, on the Matchsticks Test, PD patients performed normally not only on the copy condition, which involves constructional praxis, but also on the rotated condition, which requires, in addition, mental rotation and set-shifting from the copy condition. Thus, in the earliest stages of the disease, there is little evidence of impairment on visuospatial tasks in PD, whether or not set-shifting is involved.

The PD patients did, however, show a deficit on the Gollin Test when repeated after a delay. This deficit cannot be attributed solely to abnormal visual perception, in light of the normal performance on the earlier part of the test, or to poor declarative memory, in light of the normal ability to recall the test items after a delay. In chronic PD, studies show characteristic deficits in procedural learning, notably visual pursuit tracking (Frith *et al.*, 1986), rotary pursuit (Heindel *et al.*, 1988) and the Tower of Toronto task (Saint-Cyr *et al.*, 1988). In our study of early PD, the deficit on delayed recognition could superficially be interpreted as impaired perceptual learning. However, more detailed inspection of the learning curves (Fig. 7) shows the first trial to account for the majority of the deficit; subsequent rate of learning was normal. No unique items were given in the second test session; however, in so far as a repeated test of perception involves procedural learning, our PD patients did not show a deficit. Thus, the results of this study do not support a procedural learning deficit, at least on a visuoperceptual task, in the earliest stages of untreated PD. Moreover, the pattern of impairment on the task underlines the need to account for other cognitive deficits in performance on tests assumed to measure procedural memory.

The most striking abnormality of the PD patients on the visuospatial tasks was in the copy of the Visual Reproduction and Rey–Taylor complex figures. These tasks involve motor control, visuoperception and constructional abilities. However, the normal performance of the patients on immediate recognition of the Gollin figures and the Matchsticks Test suggests that the primary deficit contributing to poor performance in copying is disordered motor control.

Executive functions

Tasks often attributed to integrity of the frontal lobes, executive functions as they are frequently called (Pribram, 1973; Baddeley, 1986; Stuss and Benson, 1986), were impaired in our PD patient group. In the present study, tests depending heavily upon the executive functions of sequencing are Picture Arrangement, digit ordering and backward digit span, even though a clear role for the frontal lobes in task performance has not been established (Warrington *et al.*, 1986). Picture Arrangement and digit ordering have previously been found to be abnormal in chronically treated PD patients (Taylor *et al.*, 1986*b*; Sullivan *et al.*, 1989); the Picture Arrangement deficit occurred despite normal Vocabulary scores and was disproportionately great compared with performance in AD patients. The selective deficit in Picture Arrangement in PD was confirmed in the early untreated group of the present study. Although performance was exacerbated by severity of motoric deficit, it could not be completely explained by it, since PD patients differed significantly from HCS even in an untimed condition.

The normal performance of the PD patients on the Gollin and Matchsticks tests indicates that their poor scores on Picture Arrangement cannot be attributed to poor visual perception, motor control or constructional praxis and suggests that impaired Picture Arrangement in PD is attributable to a deficit of cognitive sequencing or working memory. Although a deficit in Picture Arrangement may reflect frontal lobe dysfunction, volumetric analyses of brain regions on CT scans in AD have implicated a role for the diencephalic region in performance on Picture Arrangement (Pfefferbaum *et al.*, 1990). Nevertheless, the findings are still compatible with disruption of fronto-striatal circuits in the origin of these deficits in PD.

Cognitive set-shifting deficits have been demonstrated in PD, even in early untreated cases (Lees and Smith, 1983). More recently, however, using the same shortened version of the Wisconsin Card-Sorting Test (Nelson, 1976) as used by Lees and Smith (1983), Levin *et al.* (1989) found that early PD patients showed no deficit in the ability to shift set but showed a tendency to make more perseverative errors than did control subjects. The patients in our study also showed only a trend to perseveration but no deficit in set-shifting (as judged by the number of categories achieved) except in the depressed subgroup (*see* discussion under *Depression*). The absolute scores of the PD patients were broadly comparable with published results for this patient group; the scores of our normal control group were also similar to published normal values for subjects of this age (Heaton, 1981; Levin *et al.*, 1989). The lack of a significant deficit in card-sorting performance in the PD group of this study was clearly not due to small sample size. Given that the mean scores across studies are similar, the most likely explanation of differences in levels of significance between groups lies in differences in variance, which are probably attributable to differences in heterogeneity. It is therefore important to take account of factors, such as severity of depression, that may contribute to heterogeneity of the PD group.

The only significant deficit on card sorting in the group as a whole was in the number of cards sorted before achieving the first category. This pattern of impairment involves set-formation, rather than set-shifting, and is in keeping with the abnormal McFie score which can also be regarded as a measure of set-formation deficit. Conceivably, a deficit in set-formation underlies much of the impaired card-sorting performance in PD that has traditionally been ascribed to poor set-shifting. This is particularly so in subjects who score zero categories and have thus never acquired the correct set at any point in the test. Cognitive processes involved in set-formation are speculative, but may include planning and self-ordered behaviours, motivation and arousal and the capacity to ignore distracting environmental contextual influences. The findings of impairment at the earliest stages of the disease, independent of clinical dementia and treatment, indicate that these deficits are related directly to the pathology of the disease. However, the lack of set-shifting impairment in this group, and even the relative paucity of other frontal lobe deficits, strongly suggests that cognitive dysfunction of frontal lobe type is not a necessary consequence of dopamine loss from the striatum. Our findings do not exclude more widespread frontal lobe dysfunction in chronic disease, although extrastriatal pathology may contribute to the origin of these deficits (Pillon *et al.*, 1989).

PD patients could retain and repeat as many digits from short-term memory as could normal subjects but found particular difficulty in the cognitive manipulation and ordering of such information in the Backwards Digit Span and the Digit Ordering Test. The deficits were prominent even in non-depressed patients and in patients who scored normally on a Mini Mental Status examination. The findings are compatible with other observations of impaired cognitive sequencing in PD (Sullivan *et al.*, 1989) and may relate to deficits in complex motor sequencing (Marsden, 1982; Benecke *et al.*, 1987). In addition to sequencing, tasks such as Digit Ordering, Picture Arrangement and the Brown–Peterson Distractor Task are heavily dependent on working memory. The special deficits on these types of task suggest that early untreated PD patients are most impaired at tasks dependent upon an intact working memory system.

Depression

The majority of the tests showed no difference in performance between depressed and non-depressed patients. Specifically, only McFie errors on the Picture Arrangement subtest showed any significant difference between the PD subgroups; only WCST categories and scaled score on Picture Arrangement were selectively impaired in the depressed subgroup relative to HCS, even though the PD subgroups did not differ significantly from each other. These tests are all sensitive to frontal lobe dysfunction, so the associations with depression offer tantalizing evidence of a role for fronto-limbic pathology in the depression of PD. However, the evidence is equivocal; *severity* of depression did not correlate with most measures sensitive to frontal lobe function; and scores on memory tests showed no association with depression.

The 'depressed' patients in this study were those who scored in the depressed range on the Beck Depression Inventory i.e. 14 or more; 23% of the patients fell into this subgroup. However, no patient had major depressive disorder. Furthermore, scores on the BDI may be influenced by the somatic items of the test owing to the physical rather than the affective symptoms of the disease. At most, therefore, this is a mildly depressed group of patients. Thus, although we found no major difference in cognitive performance between patients deemed depressed and non-depressed, we cannot address the relationship between cognition and affect in chronic, more severely depressed patients.

The depression of PD has been associated with slowed cerebration in a test of reaction time (Rogers *et al.*, 1987); the cognitive and affective deficits were attributed to common neurochemical pathology, degeneration of the mesocortical and mesolimbic dopamine systems. In the present study, depressed PD patients had greater motor disability but minimal difference in cognitive capacity from non-depressed patients. This discrepancy may reflect the possibility that depression in early PD is more related to psychomotor speed than to accuracy of performance. For example, Brown *et al.* (1984) demonstrated that changes in affect-arousal, which affect psychomotor speed, were associated with on–off swings in PD, but cognitive accuracy was unaffected. Measures of arousal, such as reaction time, were not of primary importance to the tasks adopted in this test battery and hence those suffering with an affective disturbance were not disproportionately compromised.

Relationship between cognition and motor control

One of the most striking findings of this study was the lack of correlation between performance on the overwhelming majority of the cognitive tests and the degree of motor disability as assessed by the KCRS and the Fine Finger Movements Test. Only those cognitive tests that depended upon motor control or visuomotor coordination showed significant correlation with motor disability that was consistent across the 2 measures of motor control. The poor correlation between cognition and motor disability was in contrast to the significant correlation between motor disability and severity of depression. As discussed above, the PD patients were, at most, mildly depressed and the BDI scores may be influenced by the somatic items of the questionnaire. Nevertheless, whilst these issues may confound interpretation of the association between depression and cognition, they do not alter the conclusion that cognition and motor disability seem to be largely unrelated in this group of early, untreated cases. We cannot exclude the possibility that meaningful correlations are undetected because of the mild nature of the deficits in both cognitive and motor domains. The findings to date, however, suggest 2 sets of dissociable processes in the earliest, clinical stages of PD: one set involves motor control and affect; deficits produce psychomotor retardation. The other set serves cognition; deficits produce impairment of short-term, working memory and attention. The association between measures of affect and motor control suggests that psychomotor retardation is based on dopaminergic pathology, whereas the cognitive deficits are largely independent of dopaminergic pathology underlying the motor disability.

CONCLUSIONS

Deficits in working memory (Fuster, 1989), short-term memory (Gardner, 1975; Fuster and Bauer, 1974) and performance on the Brown–Peterson distractor task (Stuss and Benson, 1987) follow focal frontal lobe lesions. Thus, the deficits of our early PD patients are compatible with frontal system dysfunction. In this respect, the pattern of impairment is more compatible with involvement of the orbito-frontal cortex, which may be involved in Brown–Peterson task performance (Stuss and Benson, 1987) than the dorso-lateral cortex, which supports set-shifting capacity (Milner, 1963). The pattern of deficit is also similar to that of other diseases, such as Huntington's disease and progressive supranuclear palsy, in which the pathology is predominantly subcortical and striatal lesions are prominent (reviewed in Sagar and Sullivan, 1988). To this extent, the findings are compatible with the concept of fronto-striatal pathology in the genesis of cognitive impairment in PD. It must also be acknowledged that the pattern of impairment shown in this study may simply be the initial phase of a more generalized progressive cognitive decline (Piccirilli *et al.*, 1989). Importantly, however, the weak association between motor and cognitive impairment suggests that the pathology of the early cognitive impairment is largely independent of that underlying motor impairment, that is nigrostriatal dopamine depletion. The pathological basis of the cognitive impairment in early

PD is speculative and probably multifactorial, but we propose 3 pathological mechanisms that could explain the pattern of deficit in these patients: first, lesions in other dopamine pathways (e.g. mesocortical or mesolimbic) in which the response sensitivity to dopamine is different from that of nigro-striatal pathways; secondly, non-dopaminergic lesions, involving peptide, noradrenergic, serotonergic and possibly cholinergic systems (Pillon *et al.*, 1989); and, thirdly, focal histopathological changes in the cortex that occur secondary to dysfunction in subcortical afferents. Neuronal loss in the ventral tegmental area has been found to be associated with selective neuronal loss and tangle formation in hippocampus, entorhinal cortex and orbito-frontal cortex of demented patients with parkinsonism (Torack and Morris, 1988). The findings of our study suggest that similar, if milder, pathological changes may be present in the earliest stages of Parkinson's disease without overt dementia. Longitudinal study is necessary to establish the relationship between these early behavioural changes, the later development of dementia and the underlying neuropathology.

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REFERENCES

AGID Y, RUBERG M, DUBOIS B, JAVOY-AGID F (1984) Biochemical substrates of mental disturbances in Parkinson's disease. *Advances in Neurology,* **40,** 211–218.

ALBERT ML, FELDMAN RG, WILLIS AL (1974) The 'subcortical dementia' of progressive supranuclear palsy. *Journal of Neurology, Neurosurgery, and Psychiatry,* **37,** 121–130.

ALEXANDER GE, DELONG MR, STRICK PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neuroscience,* **9,** 357–381.

AMERICAN PSYCHIATRIC ASSOCIATION (1987) *Diagnostic and Statistical Manual and Mental Disorders.* Third edition-revised. Washington, DC: American Psychiatric Association.

BADDELEY A (1986) *Working Memory.* Oxford: Clarendon Press.

BECK AT, WARD CH, MENDELSON M, MOCK J, ERBAUGH J (1961) An inventory for measuring depression. *Archives of General Psychiatry,* **4,** 561–571.

BENECKE R, ROTHWELL JC, DICK JPR, DAY BL, MARSDEN CD (1987) Disturbance of sequential movements in patients with Parkinson's disease. *Brain,* **110,** 361–379.

BLESSED G, TOMLINSON BE, ROTH M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *British Journal of Psychiatry,* **114,** 797–811.

BOLLER F, PASSAFIUME D, KEEFE NC, ROGERS K, MORROW L, KIM Y (1984) Visuospatial impairment in Parkinson's disease: role of perceptual and motor factors. *Archives of Neurology, Chicago,* **41,** 485–490.

BOWEN FP, BRADY EM, YAHR MD (1972*a*) Short and long range studies of memory, intelligence and perception in Parkinson patients treated with levodopa. In: *Parkinson's Disease,* Volume 2. Edited by J. Siegfried. Bern. Hans Huber.

BOWEN FP, HOEHN MM, YAHR MD (1972*b*) Parkinsonism: alterations in spatial orientation as determined by a route-walking test. *Neuropsychologia,* **10,** 355–361.

Bowen FP, Kamienny RS, Burns MM, Yahr MD (1975) Parkinsonism: effects of levodopa treatment on concept formation. *Neurology, Minneapolis,* **25,** 701–704.

Bowen FP, Burns MM, Brady EM, Yahr MD (1976) A note on alterations of personal orientation in parkinsonism. *Neuropsychologia,* **14,** 425–429.

Brown J (1958) Some tests of the decay theory of immediate memory. *Quarterly Journal of Experimental Psychology,* **10,** 12–21.

Brown RG, Marsden CD (1984) How common is dementia in Parkinson's disease? *Lancet,* **ii,** 1262–1265.

Brown RG, Marsden CD, Quinn N, Wyke MA (1984) Alterations in cognitive performance and affect-arousal state during fluctuations in motor function in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* **47,** 454–465.

Brown RG, Marsden CD (1986) Visuospatial function in Parkinson's disease. *Brain,* **109,** 987–1002.

Brown RG, Marsden CD (1988*a*) 'Subcortical dementia': the neuropsychological evidence. *Neuroscience,* **25,** 363–387

Brown RG, Marsden CD (1988*b*) Internal versus external cues and the control of attention in Parkinson's disease. *Brain,* **111,** 323–345.

Butters N, Barton M (1970) Effect of parietal lobe damage on the performance of reversible operations in space. *Neuropsychologia,* **8,** 205–214.

Canavan AGM, Passingham RE, Marsden CD, Quinn N, Wyke M, Polkey CE (1989) The performance on learning tasks of patients in the early stages of Parkinson's disease. *Neuropsychologia,* **27,** 141–156.

Cools AR, Van Den Bercken JHL, Horstink MWI, Van Spaendonck KPM, Berger HJC (1984) Cognitive and motor shifting aptitude disorders in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* **47,** 443–453.

Corkin S (1968) Acquisition of motor skill after bilateral medial temporal-lobe excision. *Neuropsychologia,* **6,** 255–265.

Corkin S, Growdon JH, Sullivan EV, Shedlack K (1981) Lecithin and cognitive function in aging and dementia. In: *New Approaches to Nerve and Muscle Disorders. Basic and Applied Contributions.* Edited by A. D. Kidman, J. K. Tomkins and R. A. Westerman. Amsterdam: Excerpta, Medica, pp. 229–249.

Cummings JL, Benson DF (1984) Subcortical dementia: review of an emerging concept. *Archives of Neurology, Chicago,* **41,** 874–879.

De Renzi E, Faglioni P (1978) Normative data and screening power of a shortened version of the Token Test. *Cortex,* **14,** 41–49.

De Renzi E, Ferrari C (1978) The Reporter's Test: a sensitive test to detect expression disturbances in aphasics. *Cortex,* **14,** 279–293.

de Smet Y, Ruberg M, Serdaru M, Dubois B, Lhermitte F, Agid Y (1982) Confusion, dementia and anticholinergics in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* **45,** 1161–1164.

Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW (1989) Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease. evidence for a specific attentional dysfunction. *Neuropsychologia,* **27,** 1329–1343.

Dubois B, Danzé F, Pillon B, Cusimano G, Lhermitte F, Agid Y (1987) Cholinergic-dependent cognitive deficits in Parkinson's disease. *Annals of Neurology,* **22,** 26–30

Fibiger HC (1984) The neurobiological substrates of depression in Parkinson's disease: a hypothesis. *Canadian Journal of Neurological Sciences,* **11,** 105–107.

Flowers KA, Pearce I, Pearce JMS (1984) Recognition memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* **47,** 1174–1181.

Frith CD, Bloxham CA, Carpenter KN (1986) Impairments in the learning and performance of a new manual skill in patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* **49,** 661–668.

Fuster JM (1989) *The Prefrontal Cortex: Anatomy, Physiology and Neuropsychology of the Frontal Lobe.* Second edition. New York: Raven Press.

Fuster JM, Bauer RH (1974) Visual short-term memory deficit from hypothermia of frontal cortex. *Brain Research, Amsterdam,* **81,** 393–400.

GARDNER ED (1975) *Fundamentals of Neurology. A Psychophysiological Approach.* Sixth edition. Philadelphia, PA: Saunders.

GIBB WRG, ESIRI MM, LEES AJ (1987) Clinical and pathological features of diffuse cortical Lewy body disease (Lewy body dementia). *Brain,* **110,** 1131–1153.

GOLLIN ES (1960) Developmental studies of visual recognition of incomplete objects. *Perceptual and Motor Skills,* **11,** 289–298.

GOTHAM AM, BROWN RG, MARSDEN CD (1988) 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. *Brain,* **111,** 299–321.

GROWDON JH, CORKIN S (1987) Cognitive impairments in Parkinson's disease. *Advances in Neurology,* **45,** 383–392.

HARVEY NS (1986) Psychiatric disorders in parkinsonism: 1. Functional illnesses and personality. *Psychosomatics,* **27,** 91–103.

HEATON RK (1981) *Wisconsin Card Sorting Test Manual.* Odessa, FL: Psychological Assessment Resources.

HEINDEL WC, SALMON D, BUTTERS N, SHULTS C (1988) Implicit memory in patients with Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology,* **10,** 34.

HUFF FJ, CORKIN S, GROWDON JH (1986) Semantic impairment and anomia in Alzheimer's disease *Brain and Language,* **28,** 235–249.

JAVOY-AGID F, AGID Y (1980) Is the mesocortical dopaminergic system involved in Parkinson disease? *Neurology, New York,* **30,** 1326–1330.

LEES AJ, SMITH E (1983) Cognitive deficits in the early stages of Parkinson's disease. *Brain,* **106,** 257–270.

LENNOX G, LOWE J, LANDON M, BYRNE EJ, MAYER RJ, GODWIN-AUSTEN RB (1989) Diffuse Lewy body disease: correlative neuropathology using anti-ubiquitin immunocytochemistry. *Journal of Neurology, Neurosurgery, and Psychiatry,* **52,** 1236–1247.

LEVIN BE, LLABRE MM, WEINER WJ (1989) Cognitive impairments associated with early Parkinson's disease. *Neurology, Cleveland,* **39,** 557–561.

MCFIE J, THOMPSON JA (1972) Picture arrangement: a measure of frontal lobe function? *British Journal of Psychiatry,* **121,** 547–552.

MARSDEN CD (1982) The mysterious motor function of the basal ganglia: The Robert Wartenberg Lecture. *Neurology, New York,* **32,** 514–539.

MARSDEN CD, JENNER P (1981) L-DOPA's action in Parkinson's disease. *Trends in Neurosciences,* **4,** 148–150.

MATISON R, MAYEUX R, ROSEN J, FAHN S (1982) 'Tip-of-the-tongue' phenomenon in Parkinson disease. *Neurology, New York,* **32,** 567–570.

MAYEUX R, STERN Y, ROSEN J, LEVENTHAL J (1981) Depression, intellectual impairment, and Parkinson disease. *Neurology, New York,* **31,** 645–650.

MAYEUX R, STERN Y, COTE L, WILLIAMS JBW (1984) Altered serotonin metabolism in depressed patients with Parkinson's disease. *Neurology, Cleveland,* **34,** 642–646.

MILNER B (1958) Psychological defects produced by temporal lobe excision. *Research Publications: Association for Research in Nervous and Mental Disease,* **36,** 244–257.

MILNER B (1963) Effects of different brain lesions on card sorting: the role of the frontal lobes. *Archives of Neurology, Chicago,* **9,** 90–100.

MOHR E, FABBRINI G, WILLIAMS J, SCHLEGEL J, COX C, FEDIO P *et al.* (1989) Dopamine and memory function in Parkinson's disease. *Movement Disorders,* **4,** 113–120.

MORRIS RG, DOWNES JJ, SAHAKIAN BJ, EVENDEN JL, HEALD A, ROBBINS TW (1988) Planning and spatial working memory in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* **51,** 757–766.

MORTIMER JA, PIROZZOLO FJ, HANSCH EC, WEBSTER DD (1982) Relationship of motor symptoms to intellectual deficits in Parkinson disease. *Neurology, New York,* **32,** 133–137.

MORTIMER JA, CHRISTENSEN KJ, WEBSTER DD (1985) Parkinsonian dementia. In: *Handbook of Clinical Neurology,* Volume 46. Edited by P. J. Vinken, G. W. Bruyn and H. L. Klawans. Amsterdam: Elsevier, pp. 371–384.

NELSON HE (1976) A modified card sorting test sensitive to frontal lobe defects. *Cortex,* **12,** 313–324.

NELSON HE, O'CONNELL A (1978) Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex,* **14,** 234–244.

Newcombe F (1969) *Missile Wounds of the Brain: A Study of Psychological Deficits.* London: Oxford University Press.

Osterrieth P (1944) Le test de copie d'une figure complexe. *Archives of Psychology,* **30,** 206–356.

Peterson LR, Peterson MJ (1959) Short-term retention of individual verbal items. *Journal of Experimental Psychology,* **58,** 193–198.

Petrides M, Milner B (1982) Deficits on subject-ordered tasks after frontal- and temporal-lobe lesions in man. *Neuropsychologia,* **20,** 249–262.

Pfefferbaum A, Sullivan EV, Jernigan TL, Zipursky RB, Rosenbloom MJ, Yesavage JA, Tinklenburg JR (1990) A quantitative analysis of CT and cognitive measures in normal aging and Alzheimer's disease. *Psychiatry Research: Neuroimaging,* **35,** 115–136.

Piccirilli M, D'Alessandro P, Finali G, Piccinin GL, Agostini L (1989) Frontal lobe dysfunction in Parkinson's disease: prognostic value for dementia? *European Neurology,* **29,** 71–76.

Pillon B, Dubois B, Cusimano G, Bonnet A-M, Lhermitte F, Agid Y (1989) Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? *Journal of Neurology, Neurosurgery, and Psychiatry,* **52,** 201–206.

Portin R, Rinne UK (1980) Neuropsychological responses of parkinsonian patients to long-term levodopa treatment. In: *Parkinson's disease: Current Progress, Problems and Management.* Edited by U. K. Rinne, M. Klingler and G. Stamm. Amsterdam: Elsevier, pp. 271–304.

Portin R, Rinne UK (1987) Predictive factors for cognitive deterioration and dementia in Parkinson's disease. *Advances in Neurology,* **45,** 413–416.

Portin RI, Koivusalo A, Laihinen AO, Rinne UK (1989) Cognitive deficits, motor disability and duration of illness in early Parkinson's disease. *Journal of Cinical and Experimental Neuropsychology,* **11,** 369.

Pribram KH (1973) The primate frontal cortex-executive of the brain. In: *Psychophysiology of the Frontal Lobes.* Edited by K. H. Pribram and A. R. Luria. New York: Academic Press, pp. 293–314.

Quinn NP, Rossor MN, Marsden CD (1986) Dementia and Parkinson's disease—pathological and neurochemical considerations. *British Medical Bulletin,* **42,** 86–90.

Rogers D, Lees AJ, Smith E, Trimble M, Stern GM (1987) Bradyphrenia in Parkinson's disease and psychomotor retardation in depressive illness: an experimental study. *Brain,* **110,** 761–776.

Sagar HJ (1985) Brain-behavior relationships in amnesia and dementia. In: *Senile Dementia of the Alzheimer Type.* Edited by J. T. Hutton and A. D. Kenny. New York: Alan R. Liss, pp 87–104.

Sagar HJ, Sullivan EV (1988) Patterns of cognitive impairment in dementia. In: *Recent Advances in Clinical Neurology,* Number 5. Edited by C. Kennard. Edinburgh· Churchill Livingstone, pp. 47–86.

Sagar HJ, Cohen NJ, Sullivan EV, Corkin S, Growdon JH (1988*a*) Remote memory function in Alzheimer's disease and Parkinson's disease. *Brain,* **111,** 185–206.

Sagar HJ, Sullivan EV, Gabrieli JDE, Corkin S, Growdon JH (1988*b*) Temporal ordering and short-term memory deficits in Parkinson's disease. *Brain,* **111,** 525–539.

Sahakian BJ, Morris RG, Evenden JL, Heald A, Levy R, Philpot M *et al.* (1988) A comparative study of visuospatial memory and learning in Alzheimer-type dementia and Parkinson's disease. *Brain,* **111,** 695–718.

Saint-Cyr JA, Taylor AE, Lang AE (1988) Procedural learning and neostriatal dysfunction in man. *Brain,* **111,** 941–959.

Stern Y, Mayeux R, Côté L (1984) Reaction time and vigilance in Parkinson's disease: possible role of altered norepinephrine metabolism. *Archives of Neurology, Chicago,* **41,** 1086–1089.

Stuss DT, Benson DF (1986) *The Frontal Lobes.* New York: Raven Press.

Stuss DT, Benson DF (1987) The frontal lobes and control of cognition and memory. In: *The Frontal Lobes Revisited.* Edited by E. Perecman. New York: IRBN Press, pp. 141–158.

Sullivan EV, Sagar HJ (1989) Nonverbal recognition and recency discrimination deficits in Parkinson's disease and Alzheimer's disease. *Brain,* **112,** 1503–1517.

Sullivan EV, Sagar HJ, Gabrieli JDE, Corkin S, Growdon JH (1989) Different cognitive profiles on standard behavioral tests in Parkinson's disease and Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology,* **11,** 799–820.

Sullivan EV, Sagar HJ (1991) Double dissociation of short-term and long-term memory for nonverbal material in Parkinson's disease and global amnesia: a further analysis. *Brain,* **114,** 893–906.

Taylor LB (1969) Localisation of cerebral lesions by psychological testing. *Clinical Neurosurgery,* **16,** 269–287. ✓

TAYLOR AE, SAINT-CYR JA, LANG AE (1986*a*) Frontal lobe dysfunction in Parkinson's disease: the cortical focus of neostriatal outflow. *Brain*, **109**, 845–883.

TAYLOR AE, SAINT-CYR JA, LANG AE, KENNY FT (1986*b*) Parkinson's disease and depression: a critical re-evaluation. *Brain*, **109**, 279–292.

TEUBER H-L (1976) Complex functions of basal ganglia. *Research Publications: Association for Research in Nervous and Mental Disease*, **55**, 151–168.

TORACK RM, MORRIS JC (1988) The association of ventral tegmental area histopathology with adult dementia. *Archives of Neurology, Chicago*, **45**, 497–501.

VRIEZEN ER, MOSCOVITCH M (1990) Memory for temporal order and conditional associative-learning in patients with Parkinson's disease *Journal of Clinical and Experimental Neuropsychology*, **12**, 24.

WARRINGTON EK, JAMES M, MACIEJEWSKI C (1986) The WAIS as a lateralising and localising diagnostic instrument: a study of 656 patients with unilateral cerebral lesions. *Neuropsychologia*, **24**, 223–239.

WARRIOR AS, MORTIMER JA, JUN SP, WEBSTER DD (1990) Retention of learned material in learning-impaired parkinsonians. *Journal of Clinical and Experimental Neuropsychology*, **12**, 22–23.

WECHSLER D (1955) *Wechsler Adult Intelligence Scale Manual.* New York: Psychological Corporation.

WECHSLER D, STONE CP (1945) *Wechsler Memory Scale.* San Antonio, TX: Psychological Corporation.

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FORCE AND FATIGUE IN HUMAN TYPE I MUSCLE FIBRES

A SURFACE EMG STUDY IN PATIENTS WITH CONGENITAL MYOPATHY AND TYPE I FIBRE PREDOMINANCE

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SUMMARY

An isometric ischaemic intermittent m.biceps brachii exercise test is performed by 4 patients suffering from congenital myopathies which are characterized by a 100% type I fibre predominance, and by 26 healthy volunteers. Thirty contractions per minute are made at an 80% of maximal voluntary contraction level. It is found that type I muscle fibres have a fourfold lower force-generating capacity than type II muscle fibres. The EMG amplitude shows that more EMG voltage is needed per unit force in the patients with 100% type I fibres compared with controls Under standardized fatiguing circumstances the power density frequency spectrum shows a weaker shift to lower frequencies in patients with 100% type I muscle fibres compared with controls. The muscle fibre conduction velocity (MFCV) of type I muscle fibres shows no decline during ischaemic exercise indicating an unimpaired muscle membrane excitability.

INTRODUCTION

The contribution of type I muscle fibres to the surface electromyogram (SEMG) during ischaemic isometric exercise can be studied in patients suffering from congenital myopathies, i.e. central core disease (CCD) and nemaline rod myopathy (NRM) (Linssen *et al.*, 1991). These congenital myopathies are characterized by a generalized type I fibre predominance in all skeletal muscles except for some muscles innervated by cranial nerves (Banker, 1986; Brooke, 1986). The force-generating capacity of the type I muscle fibres in patients with CCD or NRM can be estimated after correction for the differences in the estimated muscle cross-sectional area and for the non-contractile areas within the muscles of these patients. The SEMG parameters, which depend on the electrophysiological membrane properties, can be studied for the type I fibre population of these patients without interference from recruitment of type II motor units.

In the present study the force-generating capacity and the SEMG amplitude of the type I muscle fibres are measured and related to each other. Also the muscle fibre conduction velocity (MFCV), the SEMG frequency spectrum and the changes of these SEMG parameters during fatiguing isometric ischaemic m.biceps brachii exercise are studied in the type I fibre population.

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MATERIALS AND METHODS

Patients and controls

Four right-handed patients with congenital myopathy and with 100% type I fibre predominance (3 females: mean age 23.5±9.3 yrs, mean height 1.6±0.1 m, mean weight 44.0±13.6 kg; 1 male· 13 yrs, height 1.4 m and weight 29 kg) participated in an isometric ischaemic intermittent m.biceps brachii exercise test. Originally 6 patients participated in the test. Two patients were excluded because of technical problems leading to unphysiological high muscle fibre conduction velocities. Twenty-six right-handed volunteers (12 males: mean age 32.9±9.4 yrs, mean height 1.8±0.1 m, mean weight 77.2±6.9 kg; 14 females: mean age 31.9±9.7 yrs, mean height 1.7±0 m, mean weight 62.4±7.4 kg) served as a control group. All controls were in good health and without neuromuscular complaints. In controls no age-related differences in the surface EMG parameters were found (Linssen *et al.*, unpublished). No muscle biopsies were taken in controls. All subjects gave their informed consent. The committee on Experiments in Humans of the Faculty of Medicine saw and approved the experimental protocol.

Morphometry

As revealed from biopsy data (*see* Table 1) from m.soleus, m.quadriceps and m.erector trunci, 3 patients suffered from central core disease (CCD) and 1 patient suffered from adult autosomal dominant nemaline rod myopathy (NRM). The relative area of cores or rods, the percentage number of fibres containing cores, and the percentage area of fat cells were calculated by using a point-sampling procedure (*see* Fig. 3A, Linssen *et al.*, 1991).

To relate the physiological results to the gross anatomical structures of the upper arm, m.biceps skinfold measurements (Durnin and Womersley, 1974) were carried out The mean anthropometric estimated upper arm muscle-bone area (MBA) (de Koning *et al.*, 1986) was determined in most subjects. This method of anthropometric MBA estimation shows corresponding results with computer tomography estimations (de Koning *et al.*, 1986). Since the MBA measurements are standardized for the upper arm, they are expected to offer a reliable reflection of the m.biceps brachii cross-section.

Experimental set-up

The experimental protocol of the m.biceps brachii test, the way the surface electromyographic (SEMG) signals are derived from the m.biceps brachii, and the data analysis have been described previously (Linssen *et al.*, 1990, 1991). In short, first the maximal voluntary contraction level (MVC) of the right arm flexors is determined. In our experimental set-up the force generation results from a combined elbow flexion and pronation which is a cooperated biceps brachii and brachioradial muscle task. During the test intermittent isometric m.biceps brachii contractions are made at 80% of MVC under ischaemic conditions. Ischaemia is applied by a small blood pressure cuff (8 cm) wrapped around the upper arm as proximal as possible above the muscle bulk. During the ischaemic exercise the cuff remains inflated above 200 mm Hg. Thirty intermittent contractions are made per minute until the 80% MVC force level can no longer be reached. This moment is defined as the point of failure. Data analysis is performed over the performance time (PT) ending with the failure point.

Much care is taken in positioning the SEMG array parallel to the muscle fibre direction of the medial part of the right m.biceps brachii (Fig. 1A). A specially constructed surface electrode array is used which consists of 5 gold-coated electrodes, placed in-line. Four of the electrodes are used to obtain two bipolar SEMG signals in series. The distance between the electrodes is 6 mm. The electrode diameter is 2 mm. The interrecording distance between the EMG signals is 12 mm (Fig. 1B). After amplification, band pass filtering, A/D conversion, sampling and storing on magnetic disc, the SEMG signal waveform resemblance is calculated from the cross-correlation function (Arendt-Nielsen and Mills, 1985; Broman *et al.*, 1985*a*). In our test data were accepted when the maximum cross-correlation exceeded 0.7.

Data analysis

The EMG bursts during each contraction are localized by determining their maxima after rectification and rectangularly windowing the EMG over 0.5 s. The power density spectra (PDS) of the subsequent EMG bursts are calculated by using the Fast Fourier Transform algorithm. Three SEMG parameters are derived. (1) From the PDS the median frequency (Fmed) is determined; (2) the root mean square (RMS) value of the burst centre is used as a measure of the SEMG amplitude; (3) the MFCV is determined for

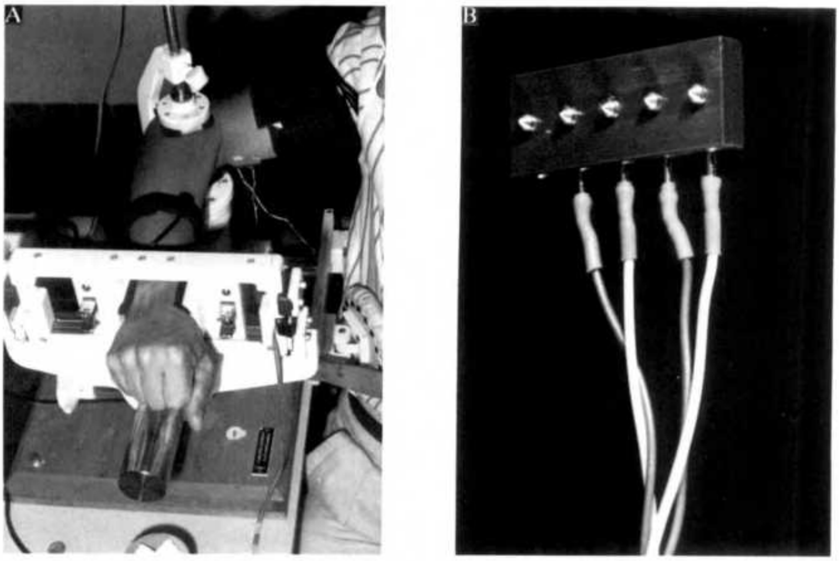

FIG. 1. A, subjects are seated and firmly attached to the biceps dynamometer. The right arm is horizontally fixed at the elbow. The hand is pronated. The elbow is nearby rectangularly flexed. The surface electrode array is positioned distally from the motor point on the medial head of the m.biceps brachii. B, detail of the surface electrode array.

each burst (Linssen *et al.*, 1990). The change of these parameters as a function of time is expressed by the 2 linear regression parameters (intercept and slope).

In order to account for the SEMG amplitude changes related to unintended differences in the exerted force for each EMG burst separately, the amplitude/force ratio ['normalized' amplitude (μV/N)] is calculated per EMG burst. The normalized amplitude vs time during the test is characterized by using a linear regression analysis. The resulting fit is presented as the mean slope (s^{-1}) over the first half and over the second half of the performance time interval. Spearman correlations and Student's *t* test are used for statistical evaluation. *P* values always express differences from controls. Results are given as mean values with (±) standard deviations.

RESULTS

Morphometry

The mean area containing cores or nemaline rods ranges from 9 to 43% with respect to the mean muscle fibre area. The amount of fatty infiltration ranges from 11 to 51% in type I patients. In Fig. 3A an example of the point-sampling grid in a patient with CCD is given. After combining these data the mean expected reduction of contractile elements per unit cross-sectional area is 46% of normal (range: 30–62%).

Skinfold and MBA measurements of m.biceps brachii

There are no significant differences between controls and patients in the subcutaneous fat layer as judged by measurements of biceps brachii skinfold (female controls: 6.5 ± 2.8 mm, male controls: 4.9 ± 1.5 mm; female type I patients: 8.7 ± 4.2 mm, male type I patient: 4 mm). The mean estimated area (MBA) of the upper arm muscles in female 100% type I patients (29.8 ± 6.5 cm^2) is significantly lower compared with

TABLE 1. MORPHOMETRIC STUDIES IN PATIENTS

Sex/age (yrs)	M/13*	F/20	F/26	F/35
Biopsy site	erect. tr	soleus	quadri	quadri
% Type I	100	100	100	100
Disease	CCD	CCD	CCD	NRM
Mean area with cores/rods per fibre (%)	9	21	43	29
Fat cell area (%)	51	11	33	13
Estimated reduction of contractile elements (%)	55	30	62	38

*Age at the time of biopsy: 1 yr.

female controls (45.3 ± 3.2 cm^2, $P < 0.001$) and reduces the expected force-generating cross-sectional area in the 100% type I fibre patients to 66% of the area in controls. The mean MBA in male controls is 54.3 ± 9.9 cm^2.

Force of arm flexors

The mean exerted force in patients with 100% type I fibres is significantly less (40.4 ± 13.9 N) compared with controls (263.7 ± 101.3 N, $P < 0.001$). This means that type I patients show a reduction of force to 15% of controls.

Muscle fibre conduction velocity

The mean initial MFCV of patients with 100% type I fibres (5.0 ± 0.5 ms^{-1}) is not significantly different from the initial MFCV in controls (4.8 ± 0.8 ms^{-1}, ns). During the biceps test the MFCV of 100% type I fibres shows on average no reduction (mean slope: 0.0 ± 0.01 ms^{-2}) compared with the mean slope of MFCV declination in controls (−0.03 ± 0.02 ms^{-2}, $P < 0.01$).

Power density frequency spectrum

The mean initial median frequency (Fmed) of the PDS distribution does not differ significantly between the type I fibre patients (100.5 ± 34.4 Hz) and controls (110.6 ± 35.0 Hz, ns). The mean slope of the Fmed decrease is −0.14 ± 0.08 $Hz.s^{-1}$ in patients with 100% type I fibres which is significantly low when compared with controls (−0.83 ± 0.50 $Hz.s^{-1}$, $P < 0.001$).

EMG amplitude

The mean initial normalized amplitude in type I patients (6.72 ± 1.56 $\mu V.N^{-1}$) is higher compared with controls (2.76 ± 1.01 $\mu V.N^{-1}$, $P < 0.001$). During the entire test period the normalized amplitude shows no change in patients (0.0 ± 0.002 s^{-1}). In controls the normalized amplitude increases (0.007 ± 0.008 s^{-1}, $P < 0.01$) during the first half of PT. During the second half of PT the normalized amplitude shows a little decline in most controls (−0.004 ± 0.014 s^{-1}, ns).

DISCUSSION

Force

The force generation in patients with 100% type I muscle fibres is much lower compared with the force in healthy volunteers. With the present histometrical and physiological

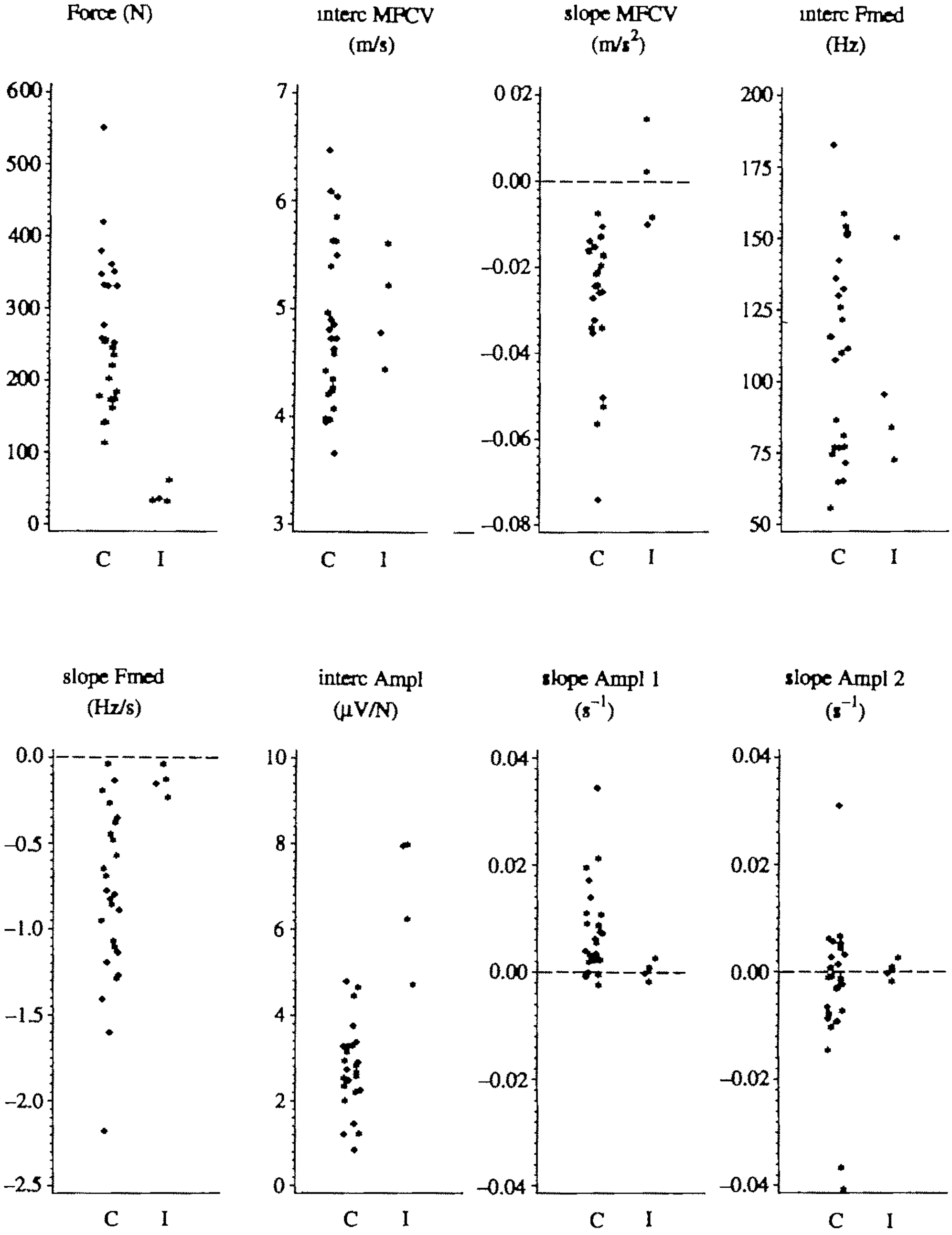

FIG. 2. Scatter diagrams giving the maximal force of the m biceps brachii and the intercepts (initial values) and slopes of the muscle fibre conduction velocity (MFCV), of the median frequency (Fmed) and of the 'normalized amplitude' (µV/N). The slope Ampl 1 and slope Ampl 2 parameters reflect the slope during the first and during the second half of the exercise interval respectively Patients with 100% type I fibres (I) are compared with controls (C). ◇ = male, * = female.

knowledge some care has to be taken in the discussion of how far the type I fibres of patients with congenital myopathies are comparable with type I fibres in normally mixed muscles, although the pathological changes in CCD and NRM, including possible abnormalities of the cytoskeletal structure in CCD (Thornell *et al.*, 1983) are essentially restricted to the core and rod zones. In the non-core and non-rod area a normal myofibrillar structure and a normal phosphorylase and oxidative-enzyme activity is found. As far as is known, the muscle fibre membranes of the type I fibres in CCD and NRM show no structural abnormalities (Banker, 1986; Brooke, 1986) (Fig. 3B).

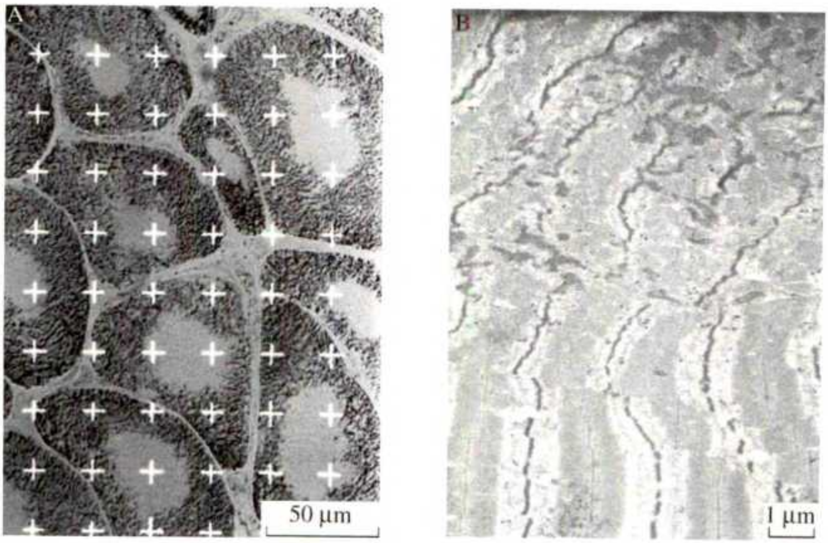

FIG. 3. A, light microscopical picture of muscle fibres with central cores (SDH-stain). The mean number of points (indicated by crosses) falling in the cores or muscle fibres are used to measure mean muscle fibre area and core area. B, transition of a normal into a core region in the myofibre. In the upper half of the micrograph distinct and irregular streaming of z-lines affecting several sarcomeres.

Our study concerning the morphological changes in the biopsied muscles thus suggest an approximately mean reduction to 54% (range 38 – 70%) of the contractile elements per unit cross-sectional area. The upper arm MBA data show that the muscle cross-sectional area in patients with 100% type I fibres is reduced to 66% of the muscle cross-sectional area of controls. The actual force generated by the pathological type I fibres is approximately 15% of the force of controls.

The results on the expected reduction of contractile elements and of the reduced muscle cross-sectional area and the fact that normal biceps muscle contains about 50% type I fibres will lead to the conclusion that type II muscle fibres are about 4 times stronger than type I fibres (see Appendix 1). This is broadly consistent with the findings from the similarly executed quadriceps femoris test (Linssen *et al.*, 1991) where type I fibres are estimated to be 5 times weaker than type II fibres.

We are aware that the present findings may be somewhat biased because no muscle biopsies were taken directly from m.biceps brachii. The amount of fatty infiltration in the biopsy specimen may be an overestimation of the fat content in the biceps brachii. Also the number of muscle fibres containing cores and/or rods may show small variations between m.biceps brachii and other muscles (Banker, 1986; Brooke, 1986). Both parameters influence the estimated percentage of muscle contractile elements. A major advantage of the present protocol is that the upper arm MBA is related to the cross-sectional area of the m.biceps brachii which makes experiments on the m.biceps brachii far more appropriate. This was the main reason for performing the present experiment. The drawback that none of the muscle biopsies was taken from the m.biceps brachii initially led us to execute the m.quadriceps femoris test. Moreover, the concordance of the results for 2 different muscles increases the force of our conclusions. Our present results support the findings of Young (1984), who reported that human type II fibres (m.quadriceps) are 3 times stronger than type I fibres.

Animal studies (Hatcher and Luff, 1985; Donselaar *et al.*, 1987; Kösler *et al.*, 1989) have also shown that type II muscle fibres produce more force than type I fibres.

Muscle fibre conduction velocity

The mean initial conduction velocity along the muscle membrane of m.biceps brachii muscle fibres in patients with 100% type I fibres does not differ significantly from controls. From the m.quadriceps experiment we would expect the initial MFCV to be lower in 100% type I patients. These differences might be due to experimental problems related to the fibre-end activity combined with the properties of the limb as a volume conductor and the subcutaneous fat layer between the surface EMG electrode on the skin and the motor units (Broman *et al.*, 1985*b*; Gootzen *et al.*, 1991). The mean upper arm subcutaneous fat layer shows no significant differences but it is relatively thicker in type I patients when related to the muscle volume of these patients. A double differential lead-off configuration is expected to cope with this problem although the superficial pick-up region connected to this approach would reduce the representiveness of the muscle as a whole (Broman *et al.*, 1985*b*).

A most significant finding is that the conduction velocity along the muscle fibre membrane of type I fibres shows no declination during the ischaemic test. This confirms the results from ischaemic m.quadriceps femoris exercise where the excitability of the muscle membrane of type I fibres, by means of MFCV measurements, remains unchanged and where the mean negative slope of MFCV vs time increases with an increasing number of type II fibres (Linssen *et al.*, 1991).

Generally, the intramuscular accumulation of lactic acid is held responsible for the decrease of the muscle membrane excitability, i.e. the slowing of the MFCV during fatiguing exercise (De Luca, 1984; Merletti *et al.*, 1984; Moritani *et al.*, 1984; Broman *et al.*, 1985*a*). The present findings are in accordance with the observations in McArdle patients who produce no lactate during anaerobic exercise and show no decline of the MFCV (Linssen *et al.*, 1990). In patients with 100% type I fibres the lactate production during IFET and during the quadriceps test is low (Linssen *et al.*, 1991). This seems to confirm the general conclusion that the lactate formation and the related reduction of MFCV during anaerobic exercise is a function of the recruitment of type II fibres (De Luca, 1984; Merletti *et al.*, 1984; Moritani *et al.*, 1984; Broman *et al.*, 1985*a*; Juel, 1988).

Power density frequency spectrum

As in the m.quadriceps test (Linssen *et al.*, 1991), the shift of the PDS to lower frequency during fatigue in type I patients underlies the shift of PDS in 85% of the controls. Many authors report on a shift of PDS to lower frequency in muscle fatigue (Bigland-Ritchie *et al.*, 1981; De Luca, 1984; Eberstein and Beattie, 1985; Moritani *et al.*, 1986; Zwarts *et al.*, 1987). In our experiment we find that the PDS expressed as Fmed, definitely shift to a lower frequency in patients and controls. During the biceps test in controls the PDS shows a steeper shift to lower frequency compared with the quadriceps test. The major mechanism which is thought to cause this shift is a decrease of the MFCV. In general, the less pronounced shift of PDS in our experiment might be explained by the fact that the MFCV shows no declination in 100% type I fibres. These findings show once more (*see also* Linssen *et al.*, 1990) that the percentage fall of Fmed usually exceeds that of MFCV (Broman *et al.*, 1985*a*; Zwarts *et al.*, 1987). The MFCV indeed cannot be the only factor determining the shift of PDS. Most probably the changing motor unit firing statistics cause the PDS to shift to lower frequencies (De Luca, 1984; Mills and Edwards, 1984; Miller *et al.*, 1987; Datta and Stephens, 1990).

EMG amplitude

The EMG amplitude is often considered as a reflection of the central drive (Bigland-Ritchie and Woods, 1984). Normally the EMG amplitude increases nearly proportionally with the exerted force (Bigland-Ritchie *et al.*, 1981; Moritani *et al.*, 1984). As in the m.quadriceps test (Linssen *et al.*, 1991), the initial EMG amplitude (μV/N) in m.biceps brachii exercise is 2.4 times higher in 100% type I patients compared with controls. When more EMG voltage is needed per unit force, this means that what can be called the 'neuromuscular efficiency' (NME) in these patients is worse by a factor of 2.4. Based on the calculations made in Appendix 2 a reduction of the NME with a factor of 4.8 can be predicted in patients. The difference can be explained with a higher absolute EMG amplitude of type II fibres. In that case it follows from straightforward calculation that the difference between the NME in normal type II fibres and normal type I fibres will be small (ratio of 1.25). As far as we know no conclusive literature for direct confirmation of this finding is available. The generally found proportional relationship between EMG amplitude and force (Milner-Brown and Stein, 1975; Bigland-Ritchie and Woods, 1984; De Luca, 1984), also for low forces (type I recruitment), indeed indicates a comparable NME for normal type I and type II fibres.

During the test the mean amplitude in patients with 100% type I fibres did not change. This supports the view that type I fibres are resistant to fatigue (Ruëgg, 1987; Sale, 1987). For comparison *see* Linssen *et al.* (1991), who showed that during quadriceps exercise, the EMG amplitude in patients with type I fibres was only slightly increased. In controls the mean amplitude shows an increase during the first half of the m.biceps test. During the second half of the test the amplitude decreases. In controls the initial EMG amplitude increase is thought to result from additional recruitment of type II fibres and an increasing motor unit firing rate. The decrease of the EMG amplitude in controls during the second part of the test is related to the declination of the MFCV (Linssen *et al.*, 1990). Simulation studies by Lateva (1988) have shown that a declination of the MFCV will cause the EMG amplitude to decrease.

Conclusion

This study shows that type I muscle fibres have less force-generating capacity than type II fibres, which seems to confirm our earlier observations in the human m.quadriceps femoris. The EMG amplitude, spectral and MFCV measurements do not support a fatiguing process in type I fibres. This suggests that muscle fatigue originates at a level out of the scope of the EMG measurements.

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REFERENCES

Arendt-Nielsen L, Mills KR (1985) The relationship between mean power frequency of the EMG spectrum and muscle fibre conduction velocity. *Electroencephalography and Clinical Neurophysiology*, **60**, 130–134.

Banker BQ (1986) The congenital myopathies. In: *Myology: Basic and Clinical.* Edited by A. G. Engel and B. Q. Banker. New York: McGraw-Hill, pp. 1527–1581.

Bigland-Ritchie B, Donovan EF, Roussos CS (1981) Conduction velocity and EMG power spectrum changes in fatigue of sustained maximal efforts. *Journal of Applied Physiology*, **51**, 1300–1305.

Bigland-Ritchie B, Woods JJ (1984) Changes in muscle contractile properties and neural control during human muscular fatigue. *Muscle and Nerve*, **7**, 691–699.

Broman H, Bilotto G, De Luca CJ (1985*a*) Myoelectric signal conduction velocity and spectral parameters: influence of force and time. *Journal of Applied Physiology*, **58**, 1428–1437.

Broman H, Bilotto G, De Luca CJ (1985*b*) A note on the noninvasive estimation of muscle fiber conduction velocity. *IEEE Transactions on Biomedical Engineering*, **32**, 341–344.

Brooke MH (1986) Congenital (more or less) muscle diseases. In: *A Clinician's View of Neuromuscular Diseases*. Second edition. Edited by M. H. Brooke. Baltimore and London: Williams and Wilkins, pp. 355–365.

Datta AK, Stephens JA (1990) Synchronization of motor unit activity during voluntary contraction in man. *Journal of Physiology*, **422**, 397–419.

De Luca CJ (1984) Myoelectrical manifestations of localized muscular fatigue in humans. *Critical Reviews in Biomedical Engineering*, **11**, 251–279.

Donselaar Y, Eerbeek O, Kernell D, Verhey BA (1987) Fibre sizes and histochemical staining characteristics in normal and chronically stimulated fast muscle of cat. *Journal of Physiology*, **382**, 237–254.

Durnin JVGA, Womersley J (1974) Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. *British Journal of Nutrition*, **32**, 77–97.

Eberstein A, Beattie B (1985) Simultaneous measurement of muscle conduction velocity and EMG power spectrum changes during fatigue. *Muscle and Nerve*, **8**, 768–773.

Gootzen THJM, Stegeman DF, Van Oosterom A (1991) Finite limb dimensions and finite muscle length in a model for the generation of electromyographic signals. *Electroencephalography and Clinical Neurophysiology.* In press.

Hatcher DD, Luff AR (1985) Force–velocity properties of fast-twitch and slow-twitch muscles of the kitten. *Journal of Physiology*, **367**, 377–385.

Juel C (1988) Muscle action potential propagation velocity changes during activity. *Muscle and Nerve*, **11**, 714–719.

Koning FL de, Binkhorst RA, Kauer JMG, Thijssen HOM (1986) Accuracy of an anthropometric estimate of the muscle and bone area in a transversal cross-section of the arm. *International Journal of Sports Medicine*, **7**, 246–249.

Kosler F, Lange F, Caffier G, Kuchler G (1989) Changes of the conduction velocity of isolated muscles induced by altered external potassium concentration. *Biomedica Biochimica Acta*, **48**, 465–470.

Lateva ZC (1988) Dependence of quantitative parameters of the extracellular potential power spectrum on propagation velocity, duration and asymmetry of action potentials. *Electromyography and Clinical Neurophysiology*, **28**, 191–203.

Linssen WHJP, Jacobs M, Stegeman DF, Joosten EMG, Moleman J (1990) Muscle fatigue in McArdle's disease: muscle fibre conduction velocity and surface EMG frequency spectrum during ischaemic exercise. *Brain*, **113**, 1779–1793.

Linssen WHJP, Stegeman DF, Joosten EMG, Binkhorst RA, Merks HJH, ter Laak HJ *et al.* (1991) Fatigue in type I fibre predominance. A muscle force and surface EMG study on the role of type I and type II muscle fibres. *Muscle and Nerve*. In press

Merletti R, Sabbahi MA, De Luca CJ (1984) Median frequency of the myoelectric signal. Effects of muscle ischemia and cooling. *European Journal of Applied Physiology*, **52**, 258–265.

Miller RG, Giannini D, Milner-Brown HS, Layzer RB, Koretsky AP, Hooper D *et al.* (1987) Effects of fatiguing exercise on high-energy phosphates, force, and EMG. evidence of three phases of recovery *Muscle and Nerve*, **10**, 810–821.

Mills KR, Edwards RHT (1984) Muscle fatigue in myophosphorylase deficiency· power spectral analysis of the electromyogram. *Electroencephalography and Clinical Neurophysiology*, **57**, 330–335.

Milner-Brown HS, Stein RB (1975) The relation between the surface electromyogram and muscular force. *Journal of Physiology*, **246**, 549–569.

Moritani T, Tanaka H, Yoshida T, Ishii C, Yoshida T, Shindo M (1984) Relationship between myoelectric signals and blood lactate during incremental forearm exercise. *American Journal of Physical Medicine*, **63**, 122–132.

Moritani T, Muro M, Nagata A (1986) Intramuscular and surface electromyogram changes during muscle fatigue. *Journal of Applied Physiology*, **60**, 1179–1185

Ruëgg JC (1987) Excitation-contraction coupling in fast- and slow-twitch muscle fibers *International Journal of Sports Medicine*, **8**, 360–364

Sale DG (1987) Influence of exercise and training on motor unit activation. *Exercise and Sport Sciences Reviews*, **15**, 95–151.

Thornell LE, Eriksson A, Edström L (1983) Intermediate filaments in human myopathies. In: *Cell and Muscle Motility*. Edited by J. W. Shay and R. M. Dowden. New York: Plenum Press, pp. 85–136.

Young A (1984) The relative isometric strength of type I and type II muscle fibres in the human quadriceps. *Clinical Physiology*, **4**, 23–32.

Zwarts MJ, van Weerden TW, Haenen HTM (1987) Relationship between average muscle fibre conduction velocity and EMG power spectra during isometric contraction, recovery and applied ischemia. *European Journal of Applied Physiology*, **56**, 212–216.

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APPENDIX 1

The estimation of the relative strength of type I fibres is based on the assumption that the force-generating capacity of the type I fibres in the non-core and non-rod areas is normal and by using the following expression·

$$fr_{I,n}F_I + fr_{II,n}F_{II} = Q(fr_{I,p}F_I + fr_{II,p}F_{II})$$

where fr_I is the fraction of type I fibres in patients (p) and controls (n), $fr_{II} = 1 - fr_I$, F_I and F_{II} are the forces generated by an area unit contractile element of type I and type II fibres respectively Q is the ratio between the estimated reduction of force and the actually measured reduction of force in type I patients compared with controls For $fr_{I,n} = 0.5$ and $fr_{I,p} = 1.0$ and for the present value of $Q = (0\ 54*0.66)/0.15 = 2\ 4$ this results in $F_{II}/F_I = 3.8$.

APPENDIX 2

Considering the 'mean' fibre of a patient (type I, 50% inactive cores or rods), it can be concluded that its force is 4 8 times lower than a size matched 'mean' control fibre (50% type I, 50% type II). Assuming that the muscle fibre membranes show equal EMG-generating characteristics, the normalized amplitude is predicted to be also 4.8 times higher in type I patients.

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AUDITORY-VISUAL ASSOCIATIONS, HEMISPHERIC SPECIALIZATION AND TEMPORAL-FRONTAL INTERACTION IN THE RHESUS MONKEY

by DAVID GAFFAN *and* SUSAN HARRISON

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SUMMARY

Monkeys (*Macaca mulatta*) learned preoperatively to associate each of 6 auditory stimuli with 1 of 6 visual stimuli. Ablation of the left prefrontal cortex in a group of 3 monkeys produced a substantial impairment in performance of the task, though performance was still above chance. Ablation of the right prefrontal cortex in a second group of 3 monkeys was without effect. Subsequently the superior temporal gyrus (auditory cortex) was removed in each animal unilaterally in the hemisphere contralateral to the existing prefrontal ablation. Ablation of the left auditory cortex produced a severe impairment, but ablation of the right auditory cortex was without effect Finally, forebrain commissurotomy in the animals with left prefrontal and right temporal ablation reduced their performance virtually to chance level. These results are consistent with previous findings indicating a left hemisphere specialization for audition in the monkey, and they give strong support to the idea, derived from previous experiments on difficult associative learning in the monkey, that auditory-visual association depends on a convergence of auditory and visual information in the prefrontal cortex.

INTRODUCTION

A number of recent experiments have suggested that, in the monkey, prefrontal cortex function is particularly important for the formation of psychologically distant associations. These are formed in associatively difficult learning tasks, where an animal is required to put together disparate sources of information. For example, Gaffan and Harrison (1988) studied a task in which the monkey had to associate coloured shapes with the temporal pattern of hand movements, an associatively difficult task. An impairment was produced in learning such associations when the visual association cortex was disconnected from the frontal cortex controlling the hand movement, by section of the anterior part of the corpus callosum combined with a unilateral ablation of visual association cortex in the hemisphere contralateral to the hand used. Eacott and Gaffan (unpublished observations) showed that the same task was impaired also by section of the uncinate fascicle, which carries information from visual association cortex to prefrontal cortex (Ungerleider *et al.*, 1989). Further confirmation of the role of prefrontal cortex in this task was obtained by Eacott and Gaffan (1990), who showed that learning of this kind could transfer interhemispherically across the anterior part of the corpus callosum. Both Gaffan and Harrison's (1988) animals and animals with uncinate fascicle section (Eacott and Gaffan, unpublished observations) were unimpaired, however, in an associatively easy task of associating visual stimuli with food reward. These findings, together with a separate set of experiments on the role of prefrontal cortex in visuo-spatial

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integration (Gaffan and Harrison, 1989), suggest the generalization that when the monkey is required to associate 2 events which are difficult to associate with each other, information about those 2 events is integrated in the prefrontal cortex.

This kind of impairment is not observed only in cross-modal associative tasks. Eacott and Gaffan (unpublished observations) showed that uncinate fascicle section also produced a severe impairment in a within-modal visual-visual association task which was associatively difficult because the 2 stimuli to be associated were spatially separate. It should also be noted that associating visual stimuli with the reward value of a food reward, which is easy for monkeys and was not impaired by uncinate fascicle section, is itself a cross-modal association task (Gaffan, 1991). However, cross-modal tasks are of particular value in exploring the validity of the generalization suggested above, because they allow different sources of information to be selectively disconnected from prefrontal cortex by selective lesions affecting the pathways of one modality or another.

One kind of cross-modal task that is clearly associatively difficult for monkeys is auditory-visual conditional discrimination learning, where the monkey must learn to use an auditory cue to guide a visual choice. Early experiments by Spaet (1944), Evarts (1952*a*,*b*), Wegener (1968) and Dewson and Burlingame (1975) established that monkeys can associate auditory with visual stimuli in this type of task, but only after thousands of trials. If the foregoing analysis can be generalized to this task, then the task should be impaired by any lesion that prevents auditory and visual information converging in the frontal lobe. The purpose of the present experiment was to test this prediction.

The analysis of auditory information flow is complicated by the factor of hemispheric specialization. Dewson *et al.* (1975) reported that 4 Rhesus monkeys with unilateral left ablation of the superior temporal gyrus suffered severe and enduring deficits in the performance of an auditory-visual conditional task, while 2 monkeys with comparable ablations in the right hemisphere showed no decrement. Heffner and Heffner (1986), using a successive auditory discrimination task, showed that 5 animals with unilateral left superior temporal gyrus ablation had a substantial impairment, while 5 animals with unilateral right superior temporal gyrus ablation all showed no effect of the lesion. Dewson *et al.*'s animals were discriminating arbitrarily chosen noises (white noise and tone) while Heffner and Heffner's were discriminating monkey calls. This set of data makes a convincing case for the specialization of the left temporal lobe in the monkey for discriminating among noises, whether naturalistic or arbitrarily constructed.

Direct projections from the auditory cortex of the superior temporal gyrus in each hemisphere to the prefrontal cortex are predominantly ipsilateral (Pandya *et al.*, 1969). Therefore, if the left superior temporal gyrus is specialized for auditory discrimination, one should expect (from the foregoing account) the left prefrontal cortex to be more important than the right prefrontal cortex for associating auditory with visual stimuli. This prediction was tested in the first stage of the present experiment. Unilateral ablations in either left or right prefrontal cortex were made in animals which had preoperatively acquired several auditory-visual associations. These were large ablations (*see* Fig. 1), intended to include all those areas of prefrontal cortex which receive information from the superior temporal gyrus (Pandya *et al.*, 1969; Jones and Powell, 1970; Chavis and Pandya, 1976).

The ablations made in stage 1 of the experiment do not, of course, make it impossible for auditory and visual information to converge in the frontal lobe. In the animals with

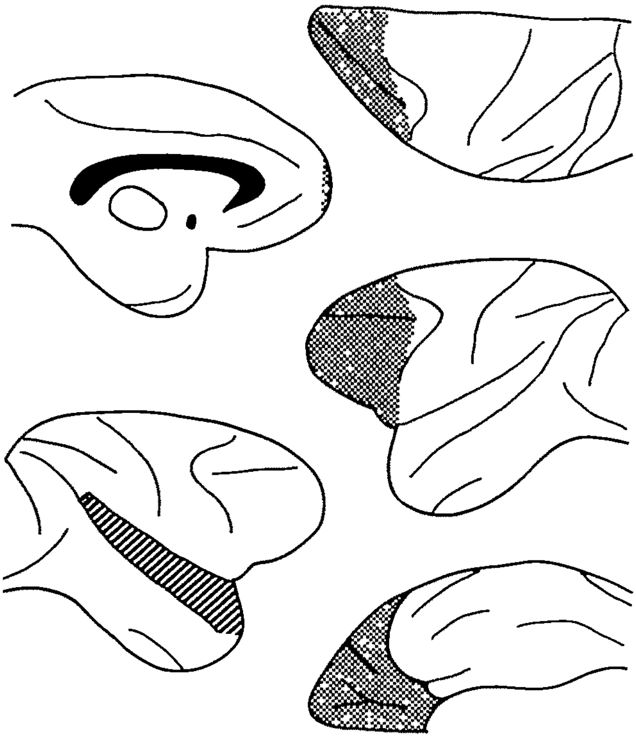

FIG 1 The intended ablation in the animals of group LF The 3 drawings on the right show the dorsal, lateral and ventral aspects of the left hemisphere, while the 2 drawings on the left show the medial aspect of the left hemisphere and the lateral aspect of the right hemisphere. In stage 1 of the experiment the left prefrontal dorsolateral and orbital cortex was removed (stippling). In stage 2 the right superior temporal gyrus was removed (hatching) In stage 3 the forebrain commissures were sectioned (black). In group RF the prefrontal ablation was in the right hemisphere, the temporal ablation was in the left hemisphere and the forebrain commissures were not sectioned.

right prefrontal lesions, auditory information from the left superior temporal gyrus can pass normally to the left prefrontal cortex; in the animals with left prefrontal lesions, there is still the possibility (among others) that auditory perceptual processing in the right temporal lobe, though inferior to the left temporal lobe, may still allow some auditory information to be passed to the right prefrontal cortex. Therefore, in stage 2 of the experiment each animal received an ablation of the superior temporal gyrus in the hemisphere contralateral to that in which the prefrontal ablation had been made (*see* Fig. 1).

Finally, in stage 3 of the experiment, the forebrain commissures were sectioned in the group of animals which had received left prefrontal and right superior temporal ablations. This was done to test the hypothesis that residual auditory-visual association in these animals might rely on heterotopic connections from the intact left superior temporal region to the right hemisphere. This hypothesis is considered in more detail in the discussion of the results, below.

The behavioural task, in preoperative training and throughout the 3 stages of postoperative tests described above, was to associate each of 6 noises with 1 of 6 coloured shapes. One trial from the task is illustrated schematically in Fig. 2. A 'sample sound' indicates that the animal should choose the shape associated with that sound; if the animal does so, the choice produces immediately a repetition of the same sound, and eventually food. The correct shape may be any of the 6 in the experiment, and on any trial it may be paired with any of the other 5 in a 2-choice discrimination trial. Details of the training schedule are presented below; the training schedule is derived from that used by Gaffan and Harrison (1987), and is designed to encourage the animals to listen to the auditory stimuli. As far as we are aware, this is the first experiment in which monkeys have learned more than 2 such auditory-visual associations.

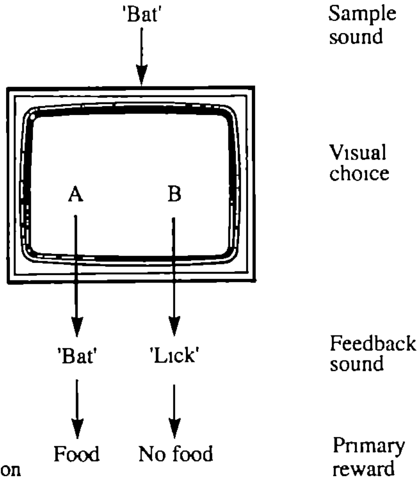

FIG 2 A trial from the behavioural task. See the text for explanation

METHODS

Subjects

Six male Rhesus monkeys (*Macaca mulatta*) took part in the experiment. All were experimentally naive at the beginning of the training schedule described below.

Surgery

All stages of surgery were carried out under aseptic conditions, and the monkeys were anaesthetized throughout surgery with barbiturate (thiopentone sodium) administered through an intravenous cannula. After each stage of surgery the animal rested for 17–21 days before resuming the behavioural task.

Stage 1. Following the completion of preoperative training, the animals were assigned to 1 of 2 groups in such a manner as to equate average preoperative ability between the groups, as far as possible. Three animals were assigned to a group receiving left prefrontal ablation and the remaining three received right prefrontal ablation. A bone flap was raised over the frontal lobe and the dura was cut to expose the whole dorsolateral surface of the lobe. The pia mater was cauterized and cut round the limits of the ablation. Cortical tissue and pia mater within these limits was then removed with a metal aspirator. As shown in Fig. 1, the intention was to remove all the cortex (including sulcal cortex) in the orbito-frontal area, together with all the cortex in the dorso-lateral area from the pole to a posterior delimiting line drawn as follows: perpendicularly from the midline to the tip of the main branch of the ascending limb of the arcuate sulcus, from there to the posterior tip of the principal sulcus, from there to the tip of the main branch of the descending limb of the arcuate sulcus, and from there in a straight line ventrally to the lateral sulcus. The tissue on the medial wall of the hemisphere was left intact, except for the extreme 2–3 mm at the frontal pole which was difficult to preserve. The dura mater was sewn, the bone flap was replaced and the wound was closed in layers.

Stage 2. Each animal received an ablation of the superior temporal gyrus in the hemisphere opposite to the existing prefrontal ablation. A bone flap was raised over the temporal lobe. The pia mater was cauterized along the superior temporal gyrus The cortex of the gyrus was removed by aspiration with a metal aspirator. Cortex in the whole of the upper bank of the superior temporal sulcus was removed up to the level of the posterior tip of the lateral sulcus. The lower bank of the lateral sulcus was also removed, up to but not including the insula. The ablation extended anteriorly to the temporal pole. The dura was sewn, the bone flap was replaced and the wound was closed in layers.

Stage 3. In the animals which had received a left prefrontal ablation in stage 1 (and therefore a right temporal ablation in stage 2) the forebrain commissures were sectioned as follows. A D-shaped bone flap was raised over the midline and the right hemisphere. The dura was cut to expose the hemisphere up to the midline. Veins draining into the sagittal sinus were cauterized and cut. The right hemisphere was retracted from the falx with a brain spoon. The corpus callosum was sectioned with a glass aspirator in the midline throughout its anterior-posterior extent. The third ventricle was entered with a narrow brain spoon (3 mm wide) and the anterior commissure was sectioned by cautery and aspiration with a thin metal aspirator (23 gauge) insulated to the tip. The dura was drawn back but not sewn, the bone flap was replaced and the wound was closed in layers

Histology

At the end of the experiment, the animals were sedated and deeply anaesthetized and perfused through the heart with saline followed by formol-saline solution. The brains were blocked in the coronal stereotaxic plane posterior to the lunate sulcus, removed from the skull, allowed to sink in sucrose-formalin solution, and sectioned coronally at 50 μm on a freezing microtome. Every fifth section through the area of the ablations (virtually the whole of the block, generating some 200 retained sections per brain) was retained, mounted on glass and stained with cresyl violet.

Fig. 3 shows the extent of the ablations in the group which received left prefrontal ablation in stage 1. Microscopic examination of the stained sections showed that the lesions in both groups were broadly as intended, as follows.

In 1 frontal lobe of each animal, no cortex was visible in the dorsolateral area anterior to the tips of the limbs of the arcuate sulcus. Cortex in the arcuate sulcus, and cortex posterior to the arcuate, was normal in appearance. Within the curve of the arcuate sulcus the lesion began before the posterior tip of the principal sulcus, and included the whole of the principal sulcus. In the orbitofrontal area, no cortex was visible except that in LF1 the most medial 3 mm of the orbital cortex, between the medial bank of the medial orbital sulcus and the inferior limit of the medial wall of the hemisphere, was spared for 4 mm of its antero-posterior extent. The anterior insula was always normal in appearance. The medial surface of the frontal lobe was normal in appearance except at the pole, where the most anterior 2–3 mm of the medial wall was never spared.

In 1 temporal lobe of each animal, the whole of the superior temporal gyrus was absent. The lesion always included the superior bank, but not the fundus, of the superior temporal sulcus. In the lateral sulcus the inferior bank was missing except that in LF3, 2–4 mm of the cortex immediately adjacent to the insula was intact over 6 mm of its antero-posterior extent. Slight unintended damage to the upper bank of the posterior tip of the lateral sulcus was seen in LF1 and LF3.

In the animals with forebrain commissurotomy the corpus callosum and the anterior commissure were sectioned. Damage to the medial wall of 1 hemisphere above the corpus callosum was observed in some places but was confined to the most inferior 2–3 mm of cingulate cortex.

Apparatus

The monkey was brought to the training apparatus in a wheeled transport cage, which was then fixed to the front of the apparatus. The monkey could reach out through bars at the front of the transport cage to touch a monitor screen which was 150 mm from the front of the cage. Coloured shapes were displayed on the monitor screen as further described below, and a system of infra-red beams and detectors indicated to the controlling computer which shape the animal had touched. Auditory stimuli as further described

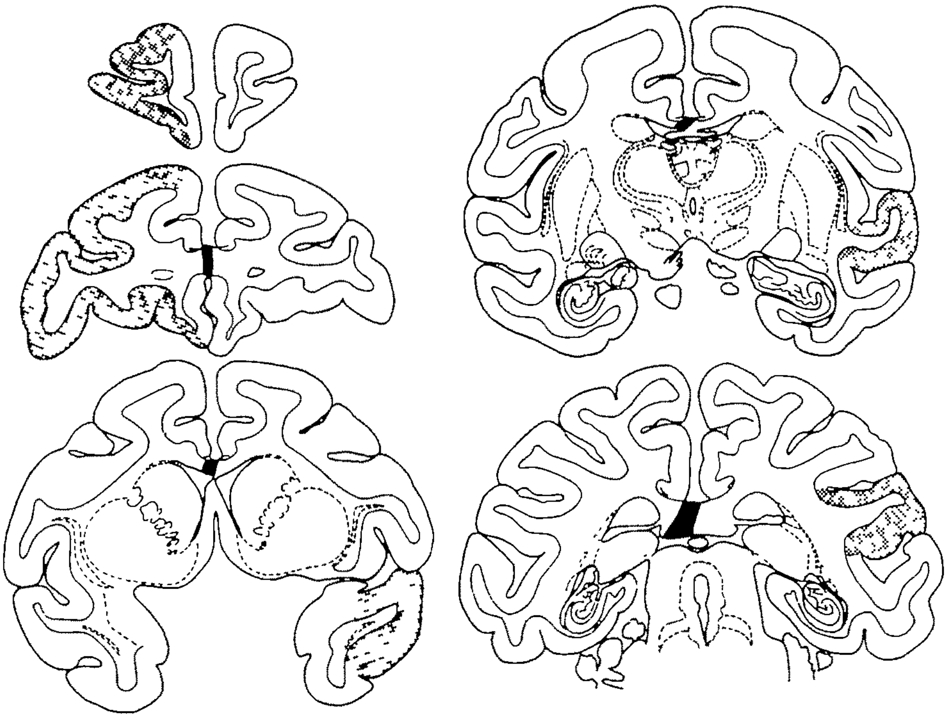

FIG 3 The extent of the lesions in the group with left prefrontal ablation, right temporal ablation and section of the forebrain commissures The cortical ablations are shown in stippling and the commissurotomy is shown in black. The 5 sections are 10 mm apart; the most posterior (lower right) is at stereotaxic zero and the most anterior (uppermost left) is 40 mm anterior to stereotaxic zero The lesions illustrated were present in all animals of this group; see the text for description of minor differences between the lesions in individual animals. The other group of animals had mirror-image ablations in the right prefrontal and left temporal cortex.

below were delivered from a loudspeaker placed centrally above and behind the monitor screen. A closed-circuit television system allowed experimenters to watch the monkey. Food rewards were delivered into a hopper placed centrally underneath the monitor screen. The food rewards were either peanuts, sugar-coated puffed rice or banana-flavoured monkey diet, according to the preference of the monkey.

The 6 coloured shapes in the experiment were constructed by superimposing 1 coloured alphabetic shape upon a different larger alphabetic shape in a different colour, for example a green Q on a large yellow X. All monkeys saw the same shapes, and the pairing of shapes with sounds was also the same for all monkeys.

The 6 sounds used in the experiment were waveforms digitized in 12 bits at 10 kHz. They were output through a low-pass 5 kHz filter, to eliminate digitization noise. The duration of each sound was 0.5 s. The sounds are here described under brief names by which they will be referred to in the analysis of behavioural results:

White noise (WN). An approximation to Gaussian white noise was produced by setting each successive value of the waveform to the average of 16 random samples from the uniform distribution of possible output voltage values. Onset and offset were tapered to avoid clicks.

A440. This was a pure sine wave at 440 Hz (concert pitch A). Onset and offset were tapered to avoid clicks.

Clicks. These were clicks at 7 Hz, beginning with a click, thus 4 clicks in 0.5 s.

Wail. The frequency of a sine wave alternated between 255 Hz and 510 Hz. The rate of the alternation cycle was 10 Hz, thus there were 5 low (middle C) notes alternating with 5 high (the octave above) notes in the 0.5 s stimulus. Onset and offset were tapered to avoid clicks.

Bat. The word 'bat' as spoken by a standard British speaker was synthesized with software derived from Klatt (1980)

Lick. The word 'lick' as spoken by a North Eastern American speaker was similarly synthesized.

Training schedule

The main experimental task was derived from that used by Gaffan and Harrison (1987). The stages of pretraining through which the animals initially went preoperatively are described below, but this main task was used throughout the main final part of preoperative training and throughout the postoperative test which followed each stage of surgery. In each daily session there were 60 pairwise trials, and each trial was presented for a variable number of subtrials. Within each successive 30 trials, each of the 6 stimuli (noise-shape pairs) was the correct choice on 5 occasions, and was paired with each of the remaining 5 stimuli as the wrong choice on 1 occasion each. Within each trial, subtrials proceeded as follows (*see* Fig. 2 for a schematic summary, but beware that the final arrow leading to food in the figure is a simplification). The subtrial began with a dot presented at the centre of the screen, and the animal had to touch the dot to proceed. The noise belonging to the correct choice (the 'sample noise') was then emitted. Two shapes appeared 0.5 s after the end of the noise. If the monkey touched the correct shape, the noise belonging to it was again emitted, a repeat of the sample noise. If the monkey touched the wrong shape, the noise belonging to that shape (a different noise from the sample noise) was emitted. Another subtrial was presented in the same way 4 s later, with the same correct stimulus and the same wrong stimulus, but with the left-right positions of the shapes freshly determined at random. Subtrials continued with the same trial in this way until 1 of 2 criteria had been fulfilled. If the monkey chose the wrong shape on 3 subtrials in succession then the trial was over, no food was dispensed, and an inter-trial interval of 30 s began. If the monkey chose the correct shape 3 times in a row than 2 food rewards were dispensed, the trial was over, and the same 30 s inter-trial interval began. Thus each trial of the 60 within each day had a minimum of 3 subtrials, and no maximum number of subtrials. The performance measure which is presented in the results below is the animal's performance on subtrial 1 of each trial.

At the beginning of preoperative training the animals were first trained to touch the screen by an automatic response-shaping procedure, which used a visual stimulus that was not used in the main task. Then they had training like the main task, but with no wrong choices possible (only the visual stimulus which was the correct choice was displayed in each trial). The number of subtrial responses required in order to end the trial and earn food rewards was increased in steps from 1 to 3. Next the wrong stimulus was introduced, but without the provision that 3 choices of it in succession would end the trial (*see above*); instead, the trial simply continued until the animal made 3 correct choices in succession. Finally, the animal was transferred to the main task.

Each animal continued preoperative training in the main task until correct choices on the first subtrial of each trial were 85% or more of the total (chance = 50%) in each of 2 successive blocks of 5 sessions of training. After each stage of surgery the animal was trained for 20 sessions.

RESULTS

Preoperative

The number of sessions which each animal took in reaching criterial performance preoperatively is shown in Table 1. The table shows the number of sessions spent in the main task (*see* Methods).

Performance in the last 5 preoperative sessions was analysed in terms of individual stimuli out of the 6 auditory-visual pairs. Table 2 shows average errors with each stimulus for each animal. Each cell is the total errors in 50 trials when that stimulus was the correct choice, plus total errors in 50 trials when that stimulus was the incorrect choice.

TABLE 1 SESSIONS TO CRITERION (S TO C) AND % ERROR AT EACH STAGE

Animal	*S to C*	*Pre*	*Post 1*	*Post 2*	*Post 3*
LF1	73	12.7	20.3	16.0	44.0
LF2	136	11.3	19.7	23.7	43.3
LF3	264	15.0	30.7	36.7	48.7
RF1	79	8.3	5.0	29.7	
RF2	116	13.0	16.3	31.0	
RF3	263	15.0	19.0	50.7	

TABLE 2. PREOPERATIVE ERROR RATES (%) WITH EACH INDIVIDUAL STIMULUS

Animal	*Lick*	*Bat*	*WN*	*Clicks*	*A440*	*Wail*
LF1	13	11	21	11	11	9
LF2	13	17	13	9	9	7
LF3	17	19	19	16	11	8
RF1	13	4	8	12	4	9
RF2	16	14	11	16	9	12
RF3	13	18	23	11	12	13
Av.	14.2	13.8	15.8	12.5	9.3	9.7

Analysis of variance of the data in Table 2 revealed a significant effect of stimuli ($F = 3.64$, df 5,25, $P < 0.05$). The effect remained significant when the test was adjusted for inequalities in the interstimulus correlation matrix (Huynh-Feldt method, epsilon = 0.7428, $P < 0.05$; Vassey and Thayer, 1987). Newman-Keuls comparisons among pairs of stimuli show that white noise was significantly more difficult than either A440 or Wail; the other paired comparisons are not significant.

The same data were also analysed as a confusion matrix, in order to test whether individual pairs of stimuli were difficult to discriminate. Table 3 shows the errors made by all animals in total with each possible stimulus pair. Each cell in Table 3 shows an observed error rate out of 120 trials. The expected error rate for each cell, shown in italics, was calculated as the average of the overall difficulty (as in Table 2) of each of the members of the pair. Thus, a discrepancy between the observed and expected value shows that performance with a pair is not predictable from the average of its members. A chi-squared test revealed that the overall discrepancies between observed and expected values were marginally significant ($\chi^2 = 15.102$, df 9, $P < 0.10$). It can be seen that the largest individual discrepancy indicates that Bat was particularly confused with Lick.

TABLE 3 ERRORS WITH EACH PAIR AT THE END OF PREOPERATIVE TRAINING

	Lick	*Bat*	*WN*	*Clicks*	*A440*
Wail	10 *14.3*	14 *14.1*	15 *15.3*	11 *13.3*	8 *11.4*
A440	7 *14.1*	13 *13.9*	16 *15.1*	12 *13.1*	
Clicks	18 *16.0*	11 *15.8*	23 *17.0*		
WN	23 *18.0*	18 *17.8*			
Bat	27 *16.8*				

Postoperative

To assess the effect of each stage of surgery we analysed performance in the last 5 sessions of the 20 sessions which followed each stage, and we compared it with the last 5 sessions of preoperative performance. Since postoperative data did not on inspection show interactions of lesion effects with individual stimuli, the following results are in terms of overall performance by each individual animal regardless of individual stimuli.

Fig. 4 shows the average performance of each group and the scores of the individuals within it. Individuals are identified in Table 1, which gives the data numerically. The group that had prefrontal ablation on the right had only 2 stages of surgery and thus 3 stages of behavioural testing including the preoperative test, while the group that had prefrontal ablation on the left had 3 stages of surgery and thus 4 stages of behavioural testing. Each individual's data point in Fig. 4 is based on 300 trials (5 sessions with 60 trials each).

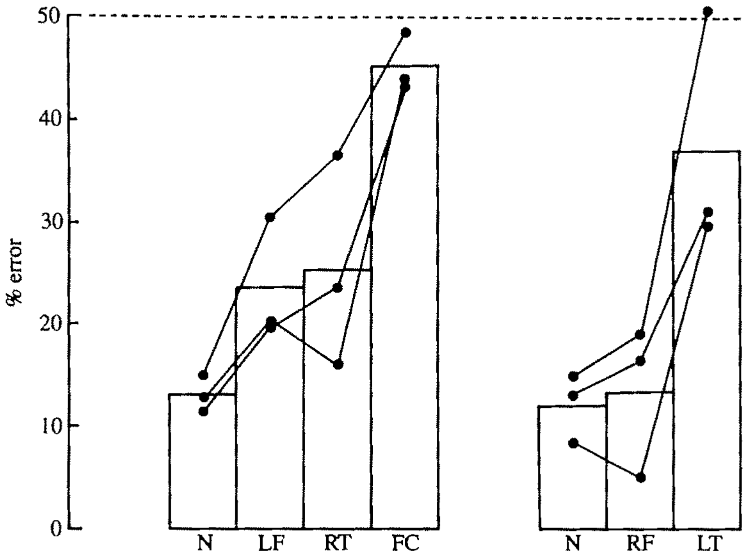

FIG. 4. Group averages (bars) and individual monkeys (dots and lines) when normal (N), after ablation of left or right prefrontal cortex (LF and RF), ablation of left or right superior temporal cortex (LT and RT) and forebrain commissurotomy (FC). The dashed line shows chance-level performance

Considering to begin with only the effect of the first stage of surgery, it can be seen that neither the left frontal nor the right frontal ablation produced a very severe impairment. Nevertheless, it can also be seen that the frontal ablation produced a greater average decrement when it was in the left hemisphere. The performance decrement (increase in error rate) between N and LF was on average 10.6 percentage points, while the decrement between N and RF was only 1.3 percentage points. The greatest individual decrement as a result of right prefrontal ablation was 4.0 percentage points, while the smallest individual decrement following left prefrontal ablation was 7.6 percentage points.

Thus there was no overlap between the 2 groups in the size of the decrement, and we can therefore conclude from a non-parametric rank-sum (Mann-Whitney) test that LF produced a greater impairment than RF ($P < 0.05$, one-tailed). A similar conclusion follows from a t test on the decrements ($t = 2.66$, df 4, $P < 0.05$, one-tailed).

Considering next the effects of temporal lobe lesions, it can be seen that ablation of the right superior temporal gyrus was virtually without effect upon the performance of the group with left prefrontal ablations (average decrement, 1.9 percentage points) while ablation of the left superior temporal gyrus produced a sharp decline in the performance of the animals with right prefrontal ablations (average decrement, 23.7 percentage points). The difference between performance with 1 prefrontal ablation and performance with the added ablation in the contralateral temporal lobe was significantly greater in the group with left temporal than in the group with right temporal lesions (by a rank-sum test, or by $t = 3.72$, df 4, $P < 0.05$, one-tailed).

Finally, it can be seen from the graph that the animals with left prefrontal and right temporal ablations were reduced virtually to chance responding by the addition of forebrain commissurotomy.

DISCUSSION

The preoperative results indicated that monkeys can learn multiple auditory-visual associations, though not easily. They also showed that individual auditory stimuli differed from each other in their effectiveness as cues for learning. White noise appeared to be a poor stimulus in this respect, being generally confused with other stimuli, while the spoken syllables ('Bat' and 'Lick') were discriminated well from other stimuli, but confused with each other. These data have obvious implications for the design of future experiments on auditory learning in monkeys.

The behavioural effects of the first stage of surgery supported the hypothesis that the left prefrontal cortex is specialized for auditory-visual association in the monkey. Right prefrontal lesions were on average without effect on the animals' performance, but left prefrontal lesions produced a significantly greater decrement than right. However, the animals still performed fairly well after left prefrontal lesions alone, scoring above 75% correct on average. In this sense, the specialization of the left prefrontal cortex for this type of association can be characterized as a weak specialization.

The second stage of surgery (unilateral auditory cortex lesions in the temporal lobe opposite to the existing prefrontal lesion) gave results consistent with the proposal that the left temporal lobe is specialized for auditory perception in the monkey. Ablation of the right superior temporal gyrus was without effect on average on the performance of the animals with left prefrontal lesions, but ablation of the left superior temporal gyrus produced a marked impairment in the animals with right prefrontal lesions, reducing their performance to below 65% correct on average.

The results from stage 2 are also of interest in elucidating the mechanism by which the animals with left prefrontal lesions alone, in the previous stage of testing, achieved their residual performance of the task. Given the evidence of left temporal specialization in auditory tasks, and given the predominantly homotopic character of the commissural connections of auditory cortex (Pandya *et al.*, 1969), one might expect that after a left prefrontal lesion information would flow from the left auditory cortex to the right auditory cortex before being integrated with visual information in the right prefrontal cortex. The negative results of ablating right auditory cortex in the second stage of surgery disprove this hypothesis, since that ablation destroys homotopic interhemispheric projections of the left auditory cortex.

The animals with left prefrontal and right temporal lesions were reduced almost to a chance level of performance by forebrain commissurotomy, in stage 3. This effect shows that their residual ability in stage 2 does depend on interhemispheric integration of information. Since the right hemisphere lacks its auditory cortex in these animals, this integration must proceed by a heterotopic route from the left auditory cortex to the right hemisphere. Some of the direct commissural projections of the auditory cortex are heterotopic (Pandya *et al.*, 1969), but it is also possible that multisynaptic pathways could carry information heterotopically from the left auditory cortex to the right hemisphere.

As noted in the introduction, hemispheric specialization in auditory learning in the monkey is a complicating factor in experiments which analyse information flow by examining disconnection effects. We have seen that the results of stage 1 in the present experiment gave evidence for a relatively weak hemispheric specialization for auditory-visual association in the left prefrontal cortex, and that the results of stage 2 were consistent with previous reports of a strong left temporal specialization for auditory discrimination. However, the hypothesis that auditory-visual association depends on the convergence of auditory and visual information in the prefrontal cortex can be assessed independently of these hypotheses concerning hemispheric specialization. All of the animals in the experiment, in both surgical groups, gave results consistent with the proposal that auditory cortex must interact with prefrontal cortex in this task.

In summary, the results give strong support to the idea that auditory-visual association in the monkey depends on a convergence of auditory with visual information in the prefrontal cortex. They also support the idea that the left hemisphere, both in temporal and frontal cortical mechanisms, is specialized for this kind of learning. The most unexpected aspect of the results was the strong performance shown by the animals with left prefrontal and right temporal lesions, which as we have seen indicates that heterotopic interhemispheric transfer from the left auditory cortex can be surprisingly efficient, although not as effective as the normal mechanism available in the left prefrontal cortex. Possibly in man also, concurrent damage to interhemispheric pathways may be important in determining the severity of impairment following damage to the left frontal cortex.

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REFERENCES

CHAVIS DA, PANDYA DN (1976) Further observations on corticofrontal connections in the Rhesus monkey. *Brain Research,* **117,** 369–386.

DEWSON JH, BURLINGAME AC (1975) Auditory discrimination and recall in monkeys. *Science,* **187,** 267–268.

DEWSON JH, BURLINGAME A, KIZER K, DEWSON S, KENNEY P, PRIBRAM KH (1975) Hemispheric asymmetry of auditory function in monkeys. *Journal of the Acoustical Society of America*, **58**, S66.

EACOTT MJ, GAFFAN D (1990) Interhemispheric transfer of visuomotor conditional learning via the anterior corpus callosum of monkeys. *Behavioural Brain Research*, **38**, 109–116.

EVARTS EV (1952*a*) Effect of ablation of prestriate cortex on auditory-visual association in monkey. *Journal of Neurophysiology*, **15**, 191–200.

EVARTS EV (1952*b*) Effect of auditory cortex ablation on auditory-visual association in monkey. *Journal of Neurophysiology*, **15**, 435–441.

GAFFAN D (1991) Amygdala and the memory of reward. In: *The Amygdala*. Edited by J. P Aggleton. New York: Wiley.

GAFFAN D, HARRISON S (1987) Amygdalectomy and disconnection in visual learning for auditory secondary reinforcement by monkeys. *Journal of Neuroscience*, **7**, 2285–2292.

GAFFAN D, HARRISON S (1988) Inferotemporal-frontal disconnection and fornix transection in visuomotor conditional learning by monkeys. *Behavioural Brain Research*, **31**, 149–163.

GAFFAN D, HARRISON S (1989) A comparison of the effects of fornix transection and sulcus principalis ablation upon spatial learning by monkeys. *Behavioural Brain Research*, **31**, 207–220.

HEFFNER HE, HEFFNER RS (1986) Effect of unilateral and bilateral auditory cortex lesions on the discrimination of vocalizations by Japanese macaques. *Journal of Neurophysiology*, **56**, 683–701.

JONES EG, POWELL TPS (1970) An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. *Brain*, **93**, 793–820.

KLATT DH (1980) Software for a cascade/parallel formant synthesizer. *Journal of the Acoustical Society of America*, **67**, 971–995.

PANDYA DN, HALLETT M, MUKHERJEE SK (1969) Intra- and interhemispheric connections of the neocortical auditory system in the rhesus monkey. *Brain Research, Amsterdam*, **14**, 49–65.

SPAET T (1944) Solution by rhesus monkeys of problems involving second-order sign behavior with intermodal cues. *Journal of Genetic Psychology*, **64**, 175–184.

UNGERLEIDER LG, GAFFAN D, PELAK VS (1989) Projections from inferior temporal cortex to prefrontal cortex via the uncinate fascicle in rhesus monkeys. *Experimental Brain Research*, **76**, 473–484.

VASEY MW, THAYER JF (1987) The continuing problem of false positives in repeated measures ANOVA in psychophysiology: a multivariate solution. *Psychophysiology*, **24**, 479–486.

WEGENER JG (1968) The effect of cortical lesions on auditory and visual discrimination behavior in monkeys. *Cortex*, **4**, 201–232.

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KINAESTHETIC ACUITY OF STUTTERERS AND NON-STUTTERERS FOR ORAL AND NON-ORAL MOVEMENTS

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SUMMARY

Six adult stutterers and six normal speakers were instructed to make the smallest possible movements of the jaw, lower lip, tongue and right index finger, both with and without continuous visual feedback. In the non-visual (kinaesthetic) condition, the stutterers showed significantly larger minimal displacements (MDs) than did the non-stutterers for oral but not for finger movements. However, movements made in the presence of visual feedback were consistently smaller for all subjects than those made without, and no differences in MD were found between the stutterers and the non-stutterers when visual feedback was provided. The results suggested the presence of a sensorimotor deficit among at least some adult stutterers that is confined to oral movements. Given the importance of somatic sensory feedback during speech production, these observed orosensory deficiencies among stutterers may provide important insights into causal factors which contribute to the breakdowns in stutterers' speech.

INTRODUCTION

It has been suggested repeatedly that the breakdowns in speech fluency of stutterers may result to some extent from a sensory feedback deficiency. Sparked by the observation that delayed auditory feedback in normal speakers often produces stuttering-like speech disfluencies (Black, 1951; Lee, 1951), most attention seems to have been focused on the role of auditory feedback distortions in stuttering (Mysak, 1960; Yates, 1963; Webster and Lubker, 1968; Van Riper, 1982; Venkatagiri, 1982).

In contrast, relatively little research has been devoted to the possible presence of kinaesthetic deficiencies in stuttering. While this may have been due to an earlier view that the contribution of such feedback during speech is minimal (Lashley, 1951; Kozhevnikov and Chistovich, 1965; MacNeilage, 1970; Hutchinson and Ringel, 1975; Perkell, 1980; Garber and Siegel, 1982), recent evidence indicates that somatic sensory mechanisms are involved in both the motor planning and execution of speech (Folkins and Abbs, 1975; Abbs and Gracco, 1981, 1983, 1984; Kelso *et al.*, 1982; Gracco and Abbs, 1989; Shaiman, 1989).

Stressing the important role of afferent information during speech production, Zimmermann (1980, 1985) hypothesized that fluency breakdowns may result from aberrant activation of brainstem reflexes triggered by sensory input generated during oral movements for speech. However, efforts aimed at detecting differences in perioral

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reflex responses between stutterers and non-stutterers have been unsuccessful (Smith and Luschei, 1983; McClean, 1989). Similarly, attempts to test the oral sensory integrity of stutterers using a variety of techniques such as oral stereognosis (Jensen *et al.*, 1975; Martin *et al.*, 1981; Stewart *et al.*, 1985); labial and lingual 2-point discrimination, intraoral and interdental weight discrimination, and interdental thickness discrimination (Jensen *et al.*, 1975); and vibrotactile magnitude production scaling (Fucci *et al.*, 1985), also have been inconclusive.

While at least some studies suggested subtle differences in oral sensation between stutterers and non-stutterers, the evidence is far from convincing. One limitation of previous studies is that the use of sensory input for *active* oral movements was not really evaluated. That is, given the inherently dynamic nature of speech production, the procedures used may have failed to assess these processes adequately (McDonald and Aungst, 1970; Bishop *et al.*, 1973; Jensen *et al.*, 1975). Indeed, it has been observed that actively controlled movements, both non-oral (Browne *et al.*, 1954; Paillard and Brouchon, 1968; McCloskey *et al.*, 1974) and oral (De Nil and Abbs, 1989), may yield greater sensory acuity compared to those that are more passively induced. These findings reinforce the suggestion that dynamic, and not static tasks, should be used to evaluate kinaesthetic acuity.

In this respect, a preliminary observation by Chuang *et al.* (1980) suggested lower movement resolution for stutterers than for non-stutterers during active oral movements. While these results were promising, the stepwise movement task they used may not have been optimal. That is, notably smaller jaw and tongue movements were obtained with normal speakers by De Nil and Abbs (1989) using a somewhat different paradigm in which discrete movements were made repeatedly from the same starting position. This observation led us to re-examine potential minimal displacement (MD) differences for actively produced jaw, lower lip and tongue movements between stutterers and normal speakers. Additionally, the MD for non-oral (i.e. finger) movements also was determined for both groups.

METHODS

Subjects

Six adult male stuttering and six adult male normally fluent speakers participated in this investigation. Informed consent, according to the Declaration of Helsinki, was obtained from all subjects. The stutterers ranged in age from 19 to 29 yrs (mean = 24 yrs). Based on the Stuttering Severity Instrument (Riley, 1980), 4 stutterers were classified as moderate, and 2 as severe. The normal subjects ranged in age from 19 to 24 yrs (mean = 21 yrs). All subjects were right handed, had a negative history of neurological or speech problems, except for the dysfluencies among the stutterers, and passed a standard hearing screening at 20 Db.

Movement task

The subjects were instructed to make the smallest possible movements up or down with their right index finger, jaw, lower lip or tongue. A 3-s 1000 Hz tone cued the onset of the movement and the subjects were told to maintian the new position until offset of the tone. Finger movements were always performed first, while the testing order of the oral articulators was counterbalanced across the 6 subjects in each of the 2 groups. A total of 30 movements (15 flexions and 15 extensions) were made with the finger. For each of the oral structures (jaw, lower lip and tongue), a randomized sequence of 50 movements (25 up and 25 down) was produced. Instructions on movement direction were given verbally prior to each movement.

All finger, jaw and lip movements started from the middle of their respective movement range, as determined by locating the upper and lower movement limits for each body part. An oscilloscope provided the subjects with visual feedback about their starting position. For the tongue, the limits of the movement range were determined by the transducer. Therefore, the starting position for this body part was defined as the middle of the transducer's maximum displacement range. Prior to making each movement, the subjects were instructed to line up the finger, jaw, lip or tongue with the starting position marked on the oscilloscope.

Feedback conditions

Because the present study was aimed at evaluating sensory integrity by measuring the ability to produce minimal displacements for active movements, it was important to eliminate the possibility that the magnitude of the movements were determined by the resolution characteristics of the efferent rather than by the afferent components of the motor control system. To this end, the movement task for each of the 4 body parts was performed in 2 conditions: with visual feedback either present (visual condition) or absent (kinaesthetic condition). The order of these 2 feedback conditions was counterbalanced across the 6 subjects in each group. Inclusion of the visual condition was based on the common observation that very small movements are possible with visual magnification. As such, if larger movements are seen in the kinaesthetic than in the visual condition, it can be assumed that the performance in the former reflects the resolution characteristics of the afferent component of the motor system.

In the visual condition, an oscilloscope was used to present the subjects with continuous visual feedback about their movements and the instruction was to make the smallest possible movements that they could *see*. An opaque shield was placed over the subject's arm to eliminate information about the movement other than that provided by the oscilloscope. Such precautions were not necessary for the oral movements in as much as they naturally occur outside the subject's visual field. The voltage gain on the oscilloscope was adjusted for each subject individually so that 1 mm of vertical transducer movement corresponded to a vertical deflection of 1 division on the CRT screen. This resulted in a uniform visual resolution and a maximum displacement of 4 mm in either direction for each of the 12 subjects.

In the kinaesthetic condition, the oscilloscope also provided visual information on the starting position, but the audible tone, which was used to cue the subject, automatically blanked the oscilloscope for the duration of the trial. In this condition, the subjects were instructed to make the smallest possible movements that they could *feel*.

Instrumentation

The subjects were seated comfortably in a dental chair with their head against a head-rest to maintain a constant visual distance from the oscilloscope throughout the experiment. For the finger movements, the subject rested the right hand on a padded inflexible bar with the thumb on top and the forearm supported horizontally in the same plane as the back of the hand. Instructions were to extend the right index finger and restrict the rotational movements to the metacarpophalangeal joint. Contact between the base of the finger and the hand-rest was carefully eliminated in order to avoid externally induced tactile touch sensations during flexion movements.

Lower lip, jaw and finger movements were recorded using strain-gauges connected to a rigid cantilever beam (a complete technical description of the transducer design has been reported by Abbs and Gilbert, 1973). The beam was inserted into a small polyethylene tube glued to the medial vermilion border of the lower lip, a splint extending from the lower teeth, or the tip of the subject's right index finger, respectively For the lip movements, a biteblock (12 mm inter-incisor distance) was placed between the subject's left molar teeth to eliminate jaw movements. None of the subjects reported awareness of the transducer during the movement task. As a result, the negligible loading force exerted by the system on the articulators during movement (Abbs and Gilbert, 1973) is unlikely to have resulted in any external sensory stimulation which may have influenced subjects' performances.

A custom-designed strain-gauge instrument was used to measure tongue movements (Fig. 1). It was placed between the subject's front teeth (14 mm inter-incisor distance), with the strain-gauge extending inside the mouth and resting on the upper surface of the tongue tip. The strain-gauge cantilever was spring-loaded so that it would easily follow tongue movements in either direction without causing interference.

Analysis

The movement signals were digitized at a sampling rate of 500 sps and digitally low-pass filtered at 20 Hz (zero lag) using a fourth order Butterworth filter implementation. Subsequently, onset of movement

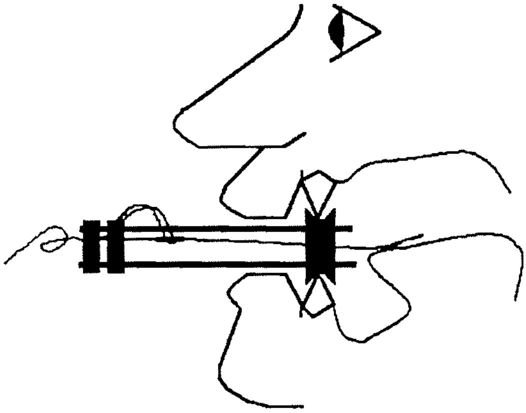

FIG. 1. Transducer used to measure minimal movements of the tongue intraorally.

was visually located and marked in each acquired signal. The first 3 movements in each direction made by the subject with his finger, jaw, lip or tongue were practice trials, and thus were not analysed. For the remaining movement signals, ensemble averages relative to movement onset were obtained using a custom-designed computer algorithm.

As illustrated in Fig. 2 for the jaw movements of 1 of the normal speakers, the mean position (in mm) was calculated for a 500 ms interval immediately prior to movement onset (= base) and a 500 ms interval during the hold-phase of the movement (= plateau). Because some slow drift in the movement signal could be observed toward the end of the tone, the plateau interval was taken from the most stable portion immediately following completion of the initial up- or downward movement. Minimal displacement (MD)

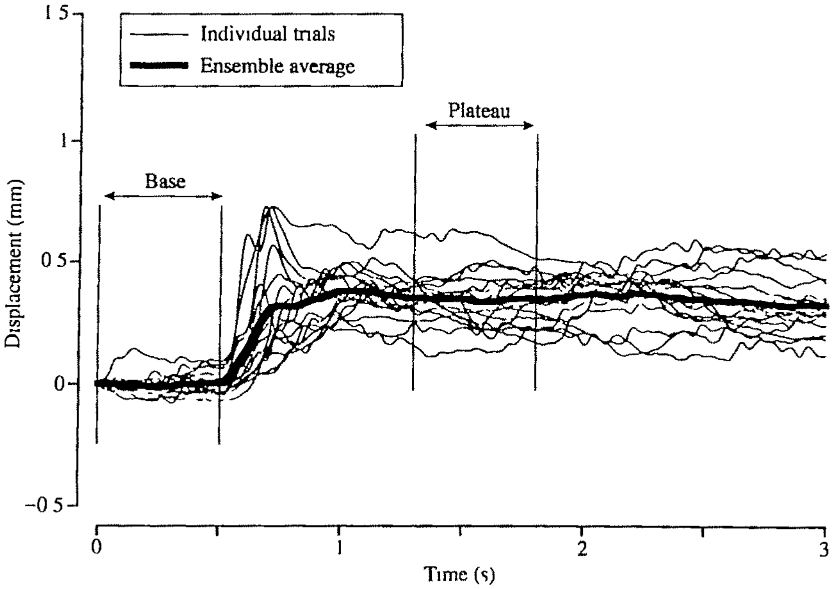

FIG. 2. Superimposed individual minimal movements of jaw movements and their ensemble average for a normal speaking subject. The minimal displacement (MD) is the difference (in mm) between the average 'base' position and the average 'plateau' position.

for each of the movements was measured as the difference between the average of the base and the plateau position (Fig. 2). This resulted in 16 MD measures per subject, representing 4 movements (finger, lip, jaw and tongue), 2 movement directions (up and down) and 2 feedback conditions (visual and kinaesthetic).

RESULTS

When the data for both the stutterers and the non-stutterers were combined, it was found that minimal movements directed superiorly, on the average, were larger than movements directed inferiorly [0.91 mm and 0.79 mm, respectively; F (1,10) = 10.19, $P = 0.01$]. However, this did not prove to be a factor that differentiated between the stutterers and the non-stutterers [F (1,10) = 0.04, $P = 0.84$] and it was decided, therefore, to combine the MDs for up and down movements in presenting the data.

Oral movements

As illustrated in Fig. 3A–C for the jaw, lower lip and tongue, respectively, the average MDs for the stutterers were consistently larger than those for the normal speakers. This difference clearly was most pronounced for the kinaesthetic condition, although somewhat larger average MDs for the stutterers also were found for the visual condition. Interestingly, of all 3 oral body parts that were tested in the kinaesthetic condition, the largest between-group MD difference was found for jaw movements (Fig. 3A).

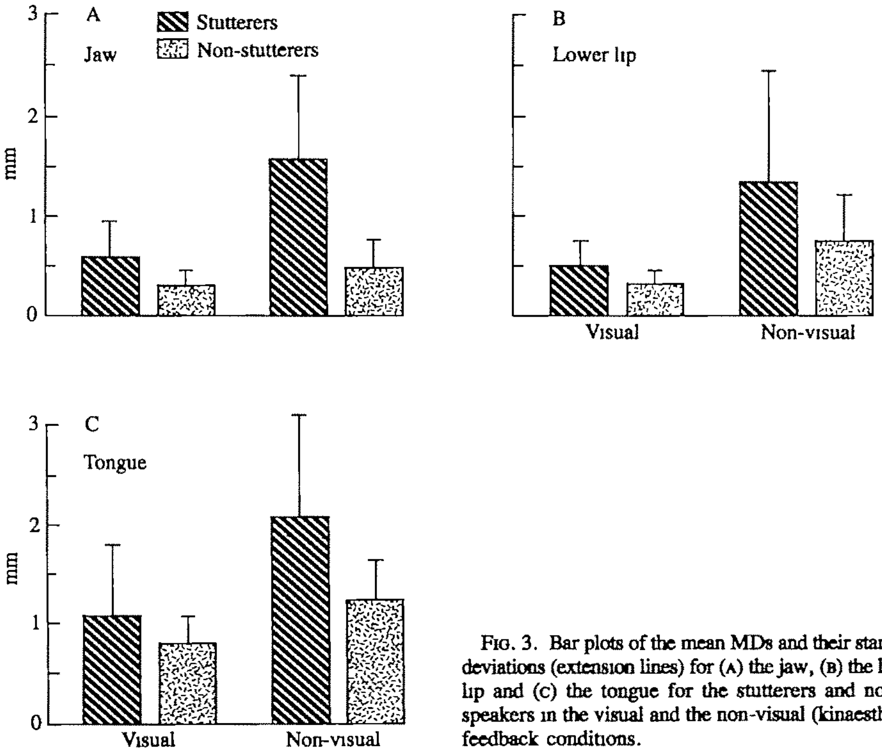

FIG. 3. Bar plots of the mean MDs and their standard deviations (extension lines) for (A) the jaw, (B) the lower lip and (C) the tongue for the stutterers and normal speakers in the visual and the non-visual (kinaesthetic) feedback conditions.

These differences in MD between the stutterers and the non-stutterers were also apparent when analysing the performances of individual subjects (Fig. 4A–C). It is important to note that the larger average MDs for the stutterers in the visual condition, as seen in Fig. 3, seem to be determined predominantly by disproportional large movements for a single subject. Indeed, the MD values obtained in this condition for all but this 1 stutterer appeared to be essentially indistinguishable from those obtained for the normal speakers.

As illustrated in Fig. 4, while an increase in MD when only kinaesthetic feedback was available could be observed for all stuttering and non-stuttering subjects, this increase often was much more dramatic for the stutterers. This manifests itself especially for jaw movements (Fig. 4A) where the MDs for 5 of the 6 stuttering subjects in the kinaesthetic condition were larger than those observed for any of the normal speakers. This stands in sharp contrast to the visual condition in which the stutterers' performance was similar to that of the normal speaking subjects. The same trend can be observed for the lip (Fig. 4B) and the tongue (Fig. 4C), although the MDs for these body parts showed more intersubject variability, especially among the stutterers.

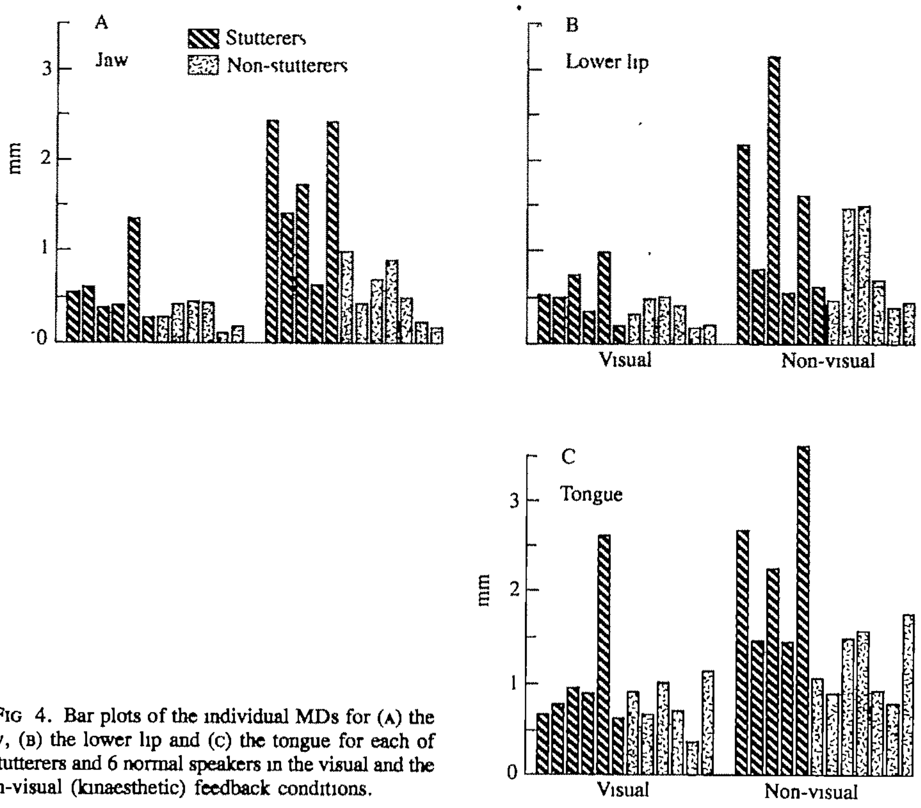

FIG 4. Bar plots of the individual MDs for (A) the jaw, (B) the lower lip and (C) the tongue for each of 6 stutterers and 6 normal speakers in the visual and the non-visual (kinaesthetic) feedback conditions.

Finger movements

In addition to movements of the jaw, lip and tongue, a comparison was also made between the MDs' of stutterers and non-stutterers for finger movements. These data are illustrated in Fig. 5A–B. Again, as for the oral movements presented earlier, a marked increase in the MDs for these non-oral movements from the visual to the kinaesthetic condition could be observed, and this for both groups. However, no difference in MD between the stutterers and the non-stutterers was observed for either the visual or the kinaesthetic condition. Indeed, the stutterers, as a group, even tended to make smaller finger movements than did the normal speakers. This lack of MD differences for finger movements between the 2 groups was also apparent for the individual subject data (Fig. 5B).

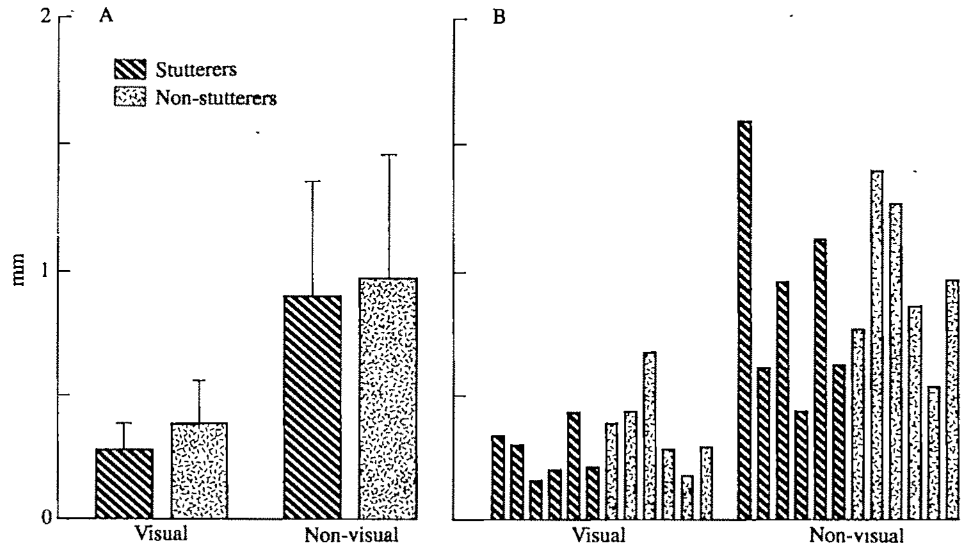

FIG 5. A, bar plots of the mean MDs and their standard deviations (extension lines) for the finger for the stutterers and non-stutterers in the visual and the non-visual (kinaesthetic) feedback conditions. B, individual movement thresholds for the finger in each condition.

Statistical analysis

A repeated measures analysis of variance (BMDP4V), blocked on subjects, was done to test the descriptive differences in MD between the 2 groups. The results of the ANOVA for the effects relevant to the present study are shown in Table 1. A significant interaction was found between movement, feedback condition and subject group [F (3,30) = 5.59, $P = 0.004$]. In other words, the MD difference between the stutterers and the non-stutterers did depend both on the specific structure that was tested (jaw, lip, tongue or finger) and on the nature of the feedback condition (visual vs kinaesthetic). This significant interaction effect was further analysed using the Tukey method of multiple comparisons. The MDs for finger movements of the stutterers and the non-stutterers did not differ statistically, regardless of the nature of the feedback available to the subjects

TABLE 1 ANALYSIS OF VARIANCE FOR REPEATED MEASURES OF THE MDs FOR ORAL AND NON-ORAL MOVEMENTS OF THE STUTTERERS AND THE NON-STUTTERERS (GROUP STUTTERERS OR NON-STUTTERERS, STRUCTURE FINGER, JAW, LOWER LIP OR TONGUE; CONDITION VISUAL OR NON-VISUAL, DIRECTION UP OR DOWN)

Group	*Df*	*SS*	*MS*	*F*	*P*
Group	1	7.23	7.23	3.38	0.095
Error	10	21.38	2.14		
Structure	3	12.75	4 25	12 88	< 0.001
Error	30	9.90	0.33		
Condition	1	19.68	19.69	28.04	< 0.001
Error	10	7.02	0.70		
Direction	1	0.64	0.64	10 19	0 010
Error	10	0.63	0.06		
Struct × Cond × Group	3	0.98	0.33	5 59	0 004
Error	30	1.77	0.06		
Struct × Direct × Group	3	0.68	0.23	2 06	0.126
Error	30	3.30	0.11		
Cond × Direct × Group	1	0.02	0.02	0.25	0 629
Error	10	0 75	0 08		
Struct × Cond × Direct × Group	3	0 52	0.17	1 69	0.191
Error	30	3 07	0 10		

(Table 2). For all the oral movements, on the other hand, the MDs obtained for the stutterers in the kinaesthetic condition were found to be significantly larger than those for the normal speakers. When visual feedback became available to the subjects, however, these differences disappeared; both the stutterers and the normal speakers showed similar movement resolution for all movements.

DISCUSSION

The purpose of the present study was to assess the kinaesthetic acuity of stutterers and normal speakers for actively produced oral and finger movements. A key observation was the presence of MD differences between the stutterers and the non-stutterers for oral but not for finger movements in the non-visual condition. Specifically, when the subjects had to rely on kinaesthetic information to assess the extent of their movements, the stutterers showed poorer oral movement resolution compared with the normal speakers. In contrast, when visual information was made available, the oral movement resolution for both groups not only became better, but, in addition, the between-group difference in MD was absent. For finger movements, on the other hand, the stuttering subjects performed similarly to the non-stutterers, regardless of the type of feedback provided.

Presumably, the minimal displacements during the visual condition were determined predominantly by the degree of visual magnification. That is, an increased magnification level would probably have resulted in even smaller active movements for most if not all of the subjects. As a result, the absolute values of the MDs in the visual condition should be interpreted cautiously. However, they constitute an important reference for

TABLE 2 STUDENTIZED RANGE STATISTIC Q (TUKEY) OF THE MDs FOR THE STUTTERERS AND THE NON-STUTTERERS IN EACH OF THE 2 FEEDBACK CONDITIONS (VISUAL OR NON-VISUAL)

		Mean MD (mm)		
Structure	*Condition*	*Stutterers*	*Controls*	*Q*
Finger	Visual	0.28	0.39	1.05
	Non-visual	0.90	0.98	0.74
Jaw	Visual	0.58	0.30	2.79
	Non-visual	1.58	0.48	11.12*
Lip	Visual	0.50	0.32	1.82
	Non-visual	1.35	0.75	6.02*
Tongue	Visual	1.07	0.79	2.87
	Non-visual	2.07	1.23	8.54*

*Significant at $\alpha = 0.01$

the MDs observed in the kinaesthetic feedback condition. The consistently smaller movements made in the presence of visual information provided evidence that the MDs in the kinaesthetic condition were determined mainly by the resolution of the somatic sensory signals generated during these movements and not by limitations of the motor system.

Similarly, the discrepancy between the MDs in the visual and the kinaesthetic feedback condition provided support for the importance of peripheral receptor mechanisms in movement sensation, and limits possible contributions of corollary discharge. The latter has been defined by McCloskey as 'internal consequences of motor commands that affect sensations, either by central modification of the processing of sensory signals generated peripherally or by their own independent actions' (McCloskey, 1981, p. 1420). Clearly, based on the present data it cannot be excluded that corollary discharge still may influence central processing of peripherally generated sensations. However, if corollary discharge were to have an important contribution to movement sensation independent from sensory input originating peripherally, one would expect to see less discrepancy between the MDs in the visual and the kinaesthetic feedback conditions.

The observation that most stutterers showed poorer non-visual movement resolution than did the non-stutterers, but only for the jaw, lip and tongue, suggests that the reduced sensory acuity among stutterers is confined to oral structures. Interestingly, a related observation has been reported by Fucci *et al.* (1985) who found that the vibrotactile magnitude scaling performance of stutterers differed significantly from that of normal speakers for the tongue but not for the hand. Based on their findings, Fucci *et al.* concluded that stuttering 'may be an internal disorder of the tactile-proprioceptive feedback mechanism that is directly involved in speech production' (Fucci *et al.*, 1985, p. 69). While methodological differences between their study and the one reported here precludes any direct comparison, the similarity of the findings seems to reinforce the possibility that a deficiency may exist in stutterers' oral sensory integrity.

The fact that the MD differences between the stutterers and the non-stutterers during the kinaesthetic feedback condition were most notable for the jaw is compatible with previous suggestions that jaw movement aberrations may play a pivotal role in stuttering. Zimmerman (1980), for instance, found that the release of a stuttering moment was often associated with a repositioning of the jaw. More recently, Alfonso *et al.* (1986)

observed that, in contrast to the complementary tongue and jaw movements observed in a normal speaker during oral closure and opening movements, stutterers relied predominantly on jaw movements. In another study, Cross and Olson (1987) analysed the jaw kinematics and voice reaction times (VRT) of stuttering and non-stuttering subjects. They concluded that the comparatively longer VRTs typically observed for stutterers (Adams *et al.*, 1985) may be the result of an asynchronous interaction between jaw movements and vocal onset.

The findings obtained in the present study reinforce the importance of understanding the central role mandibular movements may have in the speech motor control difficulties of stutterers. Moreover, they suggest that these difficulties are not purely efferent, but may involve a deficiency in the way kinaesthetic information is incorporated in the planning and execution of fine speech movements. The importance of such somatic sensory information for speech motor control has been shown convincingly for normal speakers in a number of recent investigations (Abbs and Gracco, 1983, 1984; Abbs *et al.*, 1984; Kelso *et al.*, 1984). As such, a deficiency among stutterers in incorporating precise kinaesthetic information in the motor control processes for speech may contribute significantly to a breakdown in fluency.

Site of sensory deficiency

The question arises at what level the reduction or deficiency in oral sensation among stutterers originates. One possibility may be the presence of anatomical or physiological differences in receptor mechanisms between stutterers and non-stutterers. Peripheral receptors important for kinaesthesia include muscle spindles (McCloskey, 1978; Matthews, 1982; Hulliger, 1984; Burke *et al.*, 1988) and cutaneous or mucosal mechano-receptors (Burke *et al.*, 1988; Johansson *et al.*, 1988; Edin and Abbs, 1991). At present, data concerning anatomical or physiological differences in these receptor systems between stutterers and normal speakers are lacking. However, the observation by Jensen *et al.* (1975) that stutterers and non-stutterers did not differ on 2-point discrimination tasks for the lips and tongue indirectly suggests that the density of oral cutaneous and mucosal mechano-receptors is similar for both groups, at least at these oral sites (Johansson and Vallbo, 1979; Kandel, 1985; Smith *et al.*, 1987). In contrast, Smith and Luschei (1983) have reported some data which may hint at the presence of functional differences in cutaneous and mucosal receptors between stutterers and non-stutterers. Recording EMG responses in the masseter muscle to innocuous tactile stimuli, their data revealed a greater tendency among the stutterers to show an absence of initial EMG responses to low-level stimulation. Non-stutterers, in contrast, typically showed an initial suppression of EMG activity. This observation might be interpreted cautiously as suggesting that the activation threshold level for cutaneous and mucosal mechano-receptors among stutterers may be higher than among normal speakers.

It seems more plausible that differences in non-visual MDs of stutterers and normal speakers are due to a discrepancy in the way such information is processed centrally. While direct data to test this hypothesis are not available, some indirect support comes from the observation of a general, relatively high correlation between the MDs for the finger, jaw, lip and tongue (Table 3). For both the stuttering and normal speaking subjects, large or small movements for any body part tended to be correlated positively to the MD measured in each of the other body parts. The high correlation cannot be explained

TABLE 3 CORRELATIONS BETWEEN THE MDs FOR EACH OF THE 4 BODY PARTS FOR (A) THE STUTTERERS AND (B) THE NON-STUTTERERS IN EACH OF THE 2 FEEDBACK CONDITIONS· VISUAL (UNSHADED) AND NON-VISUAL (SHADED)

A

	Finger	*Jaw*	*Lip*	*Tongue*
Finger		0 87*	0.56	0 68
Jaw	0.92**		0.81	0 94**
Lip	0.66	0.64		0.81
Tongue	0.75	0.89*	0.56	

B

	Finger	*Jaw*	*Lip*	*Tongue*
Finger		0.69	0.78	0 52
Jaw	0.75		0 97**	0.21
Lip	0.91*	0.92**		0.17
Tongue	0.76	0.29	0.53	

*Significant at $\alpha = 0\ 05$. **Significant at $\alpha = 0.01$.

based on similarities at the peripheral receptor level. Indeed, notable differences exist in the type of receptors that are available for each of the body parts tested in the present investigation (Voss, 1936; Freimann, 1954; Bowman, 1971; Dubner *et al.*, 1978; Folkins and Larson, 1978; Smith *et al.*, 1987). Therefore, a high correlation between the different movements would seem to be indicative, to some extent, of the influence of central processes which are common to all movements.

Conclusion

The present data provide evidence for the presence of a sensorimotor deficiency in orofacial movements among adult stutterers. While stutterers and non-stutterers were equally capable of making very fine oral and finger movements with visual guidance, most stutterers appear to be deficient in the use of somatic sensory information for oral movements. Given the importance of this sensory information for the control and coordination of speech movements, such a deficiency may provide significant insights into the nature and possible causal factors of speech breakdowns in stutterers.

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REFERENCES

ABBS JH, GILBERT BN (1973) A strain gage transduction system for lip and jaw motion in two dimensions: design criteria and calibration data. *Journal of Speech and Hearing Research*, **16**, 248–256.

ABBS JH, GRACCO VL (1981) Compensatory responses to low magnitude loads applied to the lower lip during speech. *Journal of the Acoustical Society of America*, **70**, Supplement 1, S78.

ABBS JH, GRACCO VL (1983) Sensorimotor actions in the control of multi-movement speech gestures. *Trends in Neurosciences*, **6**, 391–395.

ABBS JH, GRACCO VL (1984) Control of complex motor gestures: orofacial muscle responses to load perturbations of lip during speech. *Journal of Neurophysiology*, **51**, 705–723.

ABBS JH, GRACCO VL, COLE KJ (1984) Control of multimovement coordination: sensorimotor mechanisms in speech motor programming. *Journal of Motor Behavior*, **16**, 195–231.

ADAMS MR, FREEMAN FJ, CONTURE EG (1985) Laryngeal dynamics of stutterers. In: *Nature and Treatment of Stuttering: New Directions*. Edited by R. F. Curlee and W. H. Perkins. San Diego, CA: College-Hill Press, pp. 89–129.

ALFONSO PJ, WATSON BC, SEIDER RA (1986) Tongue and jaw articulation in stutterers' fluent speech. *ASHA*, **28**, No. 10, 166.

BISHOP ME, RINGEL RL, HOUSE AS (1973) Orosensory perception, speech production, and deafness. *Journal of Speech and Hearing Research*, **16**, 257–266.

BLACK JW (1951) The effect of delayed side-tone upon vocal rate and intensity. *Journal of Speech and Hearing Disorders*, **16**, 56–60.

BOWMAN JP (1971) *The Muscle Spindle and Neural Control of the Tongue. Implications for Speech.* Springfield, IL: Charles C. Thomas.

BROWNE K, LEE J, RING PA (1954) The sensation of passive movement at the metatarso-phalangeal joint of the great toe in man. *Journal of Physiology*, **126**, 448–458.

BURKE D, GANDEVIA SC, MACEFIELD G (1988) Responses to passive movement of receptors in joint, skin and muscle of the human hand. *Journal of Physiology*, **402**, 347–361.

CHUANG CK, FROMM DS, EWANOWSKI SJ, ABBS JH (1980) Nonspeech articulatory sensori-motor control differences between stutterers and nonstutterers. *ASHA*, **22**, 682.

CROSS DE, OLSON P (1987) Interaction between jaw kinematics and voice onset for stutterers and nonstutterers in a VRT task. *Journal of Fluency Disorders*, **12**, 367–380.

DE NIL LF, ABBS JH (1989) Kinesthetic thresholds during active production of orofacial and finger movements. *Society for Neuroscience Abstracts*, **15**, 397.

DUBNER R, SESSLE BJ, STOREY AT (1978) Peripheral components of motor control. In: *The Neural Basis of Oral and Facial Function.* Edited by R. Dubner, B. J. Sessle, and A. T. Storey. New York and London: Plenum press, pp. 211–245.

EDIN BB, ABBS JH (1991) Finger movement responses of cutaneous mechanoreceptors in the dorsal skin of the human hand. *Journal of Neurophysiology.* In Press.

FOLKINS JW, ABBS JH (1975) Lip and jaw motor control during speech: responses to resistive loading of the jaw. *Journal of Speech and Hearing Research*, **18**, 207–219.

FOLKINS JW, LARSON CR (1978) In search of a tonic vibration reflex in the human lip. *Brain Research, Amsterdam*, **151**, 409–412.

FREIMANN R (1954) Untersuchungen über Zahl und Anordnung der Muskelspindeln in den Kaumuskeln des Menschen. *Anatomischer Anzeiger*, **100**, 258–264.

FUCCI D, PETROSINO L, GORMAN P, HARRIS D (1985) Vibrotactile magnitude production scaling: a method for studying sensory-perceptual responses of stutterers and fluent speakers. *Journal of Fluency Disorders*, **10**, 69–75.

GARBER SR, SIEGEL GM (1982) Feedback and motor control in stuttering. In: *Learning, Speech, and the Complex Effects of Punishment.* Edited by D. K. Routh. New York: Plenum Press, pp. 93–123.

GRACCO VL, ABBS JH (1989) Sensorimotor characteristics of speech motor sequences. *Experimental Brain Research*, **75**, 586–598.

HULLIGER M (1984) The mammalian muscle spindle and its central control. *Reviews of Physiology, Biochemistry and Pharmacology*, **101**, 1–110.

HUTCHINSON JM, RINGEL RL (1975) The effect of oral sensory deprivation on stuttering behavior. *Journal of Communication Disorders*, **8**, 249–258.

JENSEN PJ, SHEEHAN JG, WILLIAMS WN, LAPOINTE LL (1975) Oral sensory-perceptual integrity of stutterers. *Folia Phoniatrica,* **27,** 38–45.

JOHANSSON RS, VALLBO ÅB (1979) Tactile sensibility in the human hand: relative and absolute densities of four types of mechanoreceptive units in glabrous skin. *Journal of Physiology,* **286,** 283–300.

JOHANSSON RS, TRULSSON M, OLSSON KÅ, ABBS JH (1988) Mechanoreceptive afferent activity in the infraorbital nerve in man during speech and chewing movements. *Experimental Brain Research,* **72,** 209–214.

KANDEL ER (1985) Central representation of touch. In: *Principles of Neural Science.* Second edition. Edited by E. R. Kandel and J. H. Schwartz. New York and Oxford· Elsevier, pp. 316–330.

KELSO JAS, TULLER B, FOWLER CA (1982) The functional specificity of articulatory control and coordination. *Journal of the Acoustical Society of America,* **72,** Supplement 1, S103.

KELSO JA, TULLER B, VATIKIOTIS-BATESON E, FOWLER CA (1984) Functionally specific articulatory cooperation following jaw perturbations during speech: evidence for coordinative structures. *Journal of Experimental Psychology: Human Perception,* **10,** 812–832.

KOZHEVNIKOV V, CHISTOVICH L (1965) Speech· articulation and perception. *Joint Publications Research Service Translation,* **30,** 543.

LASHLEY KS (1951) The problem of serial order in behavior. In: *Cerebral Mechanisms in Behavior.* Edited by L. A. Jeffress. New York and London: John Wiley, pp. 112–136.

LEE BS (1951) Artificial stutter. *Journal of Speech and Hearing Disorders,* **16,** 53–55.

MCCLEAN MD (1989) Gain and spatial characteristics of human lip-muscle reflexes. *Brain Research, Amsterdam,* **503,** 16–21.

MCCLOSKEY DI (1978) Kinesthetic sensibility. *Physiological Reviews,* **58,** 763–820.

MCCLOSKEY DI (1981) Corollary discharges: motor commands and perception. In: *Handbook of Physiology,* Section 1, Volume 2, Part 2. Edited by J. M. Brookhart and V. B. Mountcastle. Bethesda, MD· American Physiological Society, pp. 1415–1447.

MCCLOSKEY DI, EBELING P, GOODWIN GM (1974) Estimation of weights and tensions and apparent involvement of a 'sense of effort'. *Experimental Neurology,* **42,** 220–232.

MCDONALD ET, AUNGST LF (1970) Apparent independence of oral sensory functions and articulatory proficiency. In: *Second Symposium on Oral Sensation and Perception.* Edited by J. F. Bosma. Springfield, IL: Charles C. Thomas, pp. 391–397.

MACNEILAGE PF (1970) Motor control of serial ordering of speech. *Psychological Review,* **77,** 182–196.

MARTIN RR, LAWRENCE BA, HAROLDSON SK, GUNDERSON D (1981) Stuttering and oral stereognosis. *Perceptual and Motor Skills,* **53,** 152–162.

MATTHEWS PBC (1982) Where does Sherrington's 'muscular sense' originate? Muscles, joints, corollary discharges? *Annual Review of Neuroscience,* **5,** 189–218.

MYSAK ED (1960) Servo theory and stuttering. *Journal of Speech and Hearing Disorders,* **25,** 188–195.

PAILLARD J, BROUCHON M (1968) Active and passive movements in the calibration of position sense. In: *The Neuropsychology of Spatially Oriented Behavior.* Edited by S. J. Freedman. Homewood, IL: Dorsey Press, pp. 37–55.

PERKELL JS (1980) Phonetic features and the physiology of speech production. In: *Language Production.* Edited by B. Butterworth. London: Academic Press, pp. 337–372.

RILEY GD (1980) *Stuttering Severity Instrument.* Tigard, Oregon: C.C. Publications.

SHAIMAN S (1989) Kinematic and electromyographic responses to perturbation of the jaw. *Journal of the Acoustical Society of America,* **86,** 78–88.

SMITH A, LUSCHEI ES (1983) Assessment of oral-motor reflexes in stutterers and normal speakers: preliminary observations. *Journal of Speech and Hearing Research,* **26,** 322–328.

SMITH A, MCFARLAND DH, WEBER CM, MOORE CA (1987) Spatial organization of human perioral reflexes. *Experimental Neurology,* **98,** 233–248.

STEWART C, EVANS WB, FITCH JL (1985) Oral form perception skills of stuttering and nonstuttering children measured by stereognosis. *Journal of Fluency Disorders,* **10,** 311–316.

VAN RIPER C (1982) *The Nature of Stuttering.* Second edition. Englewood Cliffs, NJ: Prentice-Hall.

VENKATAGIRI HS (1982) A comparison of DAF-induced disfluencies with stuttering. *Journal of Communication Disorders,* **15,** 385–393.

VOSS H (1936) Ein besonders reichliches Vorkommen vos Muskelspindeln in der tiefen Portion des M.masseter des Menschen und der Anthropoiden. *Anatomischer Anzeiger,* **81,** 290–292.

WEBSTER RL, LUBKER BB (1968) Masking of auditory feedback in stutterers' speech. *Journal of Speech and Hearing Research,* **11,** 221–223.

YATES AJ (1963) Recent empirical and theoretical approaches to the experimental manipulation of speech in normal subjects and in stammerers. *Behavioural Research and Therapy,* **1,** 95–119.

ZIMMERMANN G (1980) Articulatory dynamics of fluent utterances of stutterers and nonstutterers. *Journal of Speech and Hearing Research,* **23,** 95–107.

ZIMMERMANN G (1985) Articulatory dynamics of stutterers. In: *Nature and Treatment of Stuttering: New Directions.* Edited by R. F. Curlee and W. H. Perkins. San Diego, CA: College-Hill Press, pp. 131–147.

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MAN IN MOTION

HISTORICAL AND CLINICAL ASPECTS OF VESTIBULAR FUNCTION*

A REVIEW

by THOMAS BRANDT

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SUMMARY

This is a review of selected aspects of the history of the vestibular system (J. E. Purkyne, E. Mach, A. Crum-Brown) and of our current understanding of vestibular malfunction in clinical vertigo syndromes.

Evidence is presented for a preliminary classification of central vestibular brainstem syndromes according to the three major planes of action of the vestibulo-ocular reflex (VOR): (1) disorders of the VOR in the horizontal (yaw) plane (horizontal nystagmus, pseudo 'vestibular neuritis'); (2) disorders of the VOR in the sagittal (pitch) plane (downbeat nystagmus; upbeat nystagmus); (3) disorders of the VOR in the frontal (roll) plane (ocular tilt reaction; lateropulsion).

The pathophysiology of peripheral vestibular disorders is discussed: a specific gravity differential between the cupula fluid and the endolymph (buoyancy mechanism) causes vertigo in benign paroxysmal positioning vertigo and positional alcohol nystagmus. Vestibular neuritis is probably a partial unilateral vestibular paralysis due to viral infection of the superior division of the nerve trunk. The common post-traumatic vertigo is explained by otolith dysfunction secondary to dislodged otoconia resulting in unequal loads on the macula beds and a tonus imbalance between the two otoliths.

INTRODUCTION

The title 'Man in Motion' is ambiguous. It could apply either to a description of locomotion provided by an external observer, or to the subjective sensations experienced by the individual in motion.

More pretentiously, and in a figurative sense, man in motion is a metaphor for human development related to evolution or history. In the mundane sense, however, for neurologists 'man in motion' is simply related to the question of how we move and how we control movement by sensorimotor control of equilibrium and locomotion and its disorders.

The detection of body motion (linear and angular accelerations) and the position of the head in space relative to the gravitational vector is the responsibility of the vestibular system. Unusual motion stimulation or lesional dysfunction cause vestibular vertigo syndromes, which are commonly characterized by a combination of phenomena involving perceptual, ocular motor, postural and vegetative manifestations: vertigo, nystagmus, ataxia and nausea (Brandt and Daroff, 1980*a*). Neurology of the vestibular system includes peripheral labyrinthine and central vestibular vertigo syndromes.

I would like to approach the neurology of the vestibular system via a short look at the history of vestibular physiology. Following this, a slightly altered concept of

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cupulolithiasis will be presented, which rejects gravity as the main cause of benign paroxysmal positioning vertigo, the commonest labyrinthine vertigo syndrome. Thereafter, a preliminary and speculative classification of central vestibular brainstem disorders is proposed according to the major planes of action of the vestibulo-ocular reflex. Finally, an attempt is made to discuss the possible role of the otoliths in hitherto widely neglected and poorly described clinical syndromes.

HISTORY OF AN ANCIENT SENSORY SYSTEM

The vestibular system of the vertebrates is, in evolutionary terms, ancient, with its roots in the graviceptive statocysts of coelenterates. Its clinical history, however, encompasses little more than 100 yrs. Despite beautiful anatomical preparations of the labyrinth in the early 19th century, the conception prevailed that body accelerations were primarily sensed by the distribution of blood or by pressure receptors in the skin (Henn and Young, 1975).

There was a remarkable group of 19th-century scientists, among them Jan Evangelista Purkyne, Ernst Mach, Josef Breuer, Hermann Helmholz and Alexander Crum-Brown who discovered the methods of sensing motion and laid the foundation of modern vestibular and oculomotor research (Cohen, 1984*a*).

Jan Evangelista Purkyne, born 1787 in Northern Bohemia was a leading figure in cultural and social life in Prague. He founded the doctrine of 'exact subjectivism', being a most careful observer in his psychophysical experiments (Grüsser, 1984). His contributions to the physiology of vision, the oculomotor and the vestibular system are well recognized. Not only was he the first to describe the Purkyne 'images' of the anterior and posterior surfaces of cornea and the lens, he also described optokinetic nystagmus and optokinetic after-nystagmus, and by use of a rotary chair explained movement after-effects as an habituation of the gaze motor system. In these times rotary chairs and centrifuges were used in the treatment of psychiatric patients. Important as his contributions were to the physiology of the vestibular system he did not propose the existence of peripheral receptors in the labyrinth. He believed that direct mechanical effects on certain parts of the brain, especially the cerebellum, were responsible for the mechanisms of vertigo (Grüsser, 1984).

Ernst Mach was also born in Bohemia in 1838, which at that time was part of the Austrian Empire. He studied in Vienna and later, after 27 yrs in Prague, at the age of 57 became professor of philosophy in Vienna in 1895 (Henn and Young, 1975). In 1873 Mach published three papers on the sense of equilibrium in the Proceedings of the Vienna Academy of Sciences which were later, in 1875, published as the famous book, *Grundlinien der Lehre von den Bewegungsempfindungen* (Fundamentals of the theory of motion perception) (Henn, 1984). His experiments were mostly psychophysical and included measurements of thresholds and visual-vestibular interaction. Using a revolving chair Ernst Mach as well as Josef Breuer and Alexander Crum-Brown all suggested that the parameter that is sensed during rotation is acceleration and they strongly supported the hypothesis that the sensory organ is the labyrinth. Mach and Crum-Brown presented evidence that the appropriate physiological stimulus is a pressure difference across the cupula acting during acceleration. This was specifically contrary to the sustained endolymph flow theory of Breuer (Henn, 1984).

Alexander Crum-Brown published a famous paper 'On the sense of rotation and the anatomy and physiology of the semicircular canals of the internal ear' in the *Journal of Anatomy and Physiology* in 1874. He came to conclusions about the function of the labyrinth that are still valid (Henn, 1984). This was long before the pathophysiology of vestibular disorders was understood.

If one asks for the name of the most knowledgeable and influential contemporary physician in the study of labyrinthine malfunction, the most likely suggestion would be the otolaryngologist *Harold Schuknecht*. He has presented controversial hypotheses and experimental evidence in the explanation of the three most common forms of labyrinthine vertigo: benign paroxysmal positioning vertigo, vestibular neuritis and Menière's disease.

Schuknecht postulated a mechanical mechanism termed 'cupulolithiasis' (Schuknecht, 1969) for benign paroxysmal positioning vertigo, which was intially described by Bárány in 1921. He argued that, when the head is upright, inorganic particles, detached from the otoconial layer by spontaneous degeneration or head trauma, gravitate to and become settled on the cupula of the posterior semicircular canal, which is situated directly inferior to the utricle. In fact he found basophilic deposits on the cupula of the precipitating posterior canal in individual patients (Schuknecht and Ruby, 1973).

In vestibular neuritis [first described by Ruttin (1909) and the term coined by Hallpike (1949)] Schuknecht and Kitamura (1981) found cell degeneration of one or more vestibular nerve trunks in post-mortem studies, which suggest that the cause may be a viral infection of the vestibular nerve, similar to those producing Bell's palsy and sudden sensorineural hearing loss.

In Menière's disease (first described by Menière in 1861) Schuknecht investigated the relationship between scarring labyrinthitis or blockage of the endolymph flow and endolymphatic hydrops (Schuknecht and Gulya, 1983). He explained the frequently benign course of Menière's disease. A permanent fistula of the membranous labyrinth, spontaneous or surgical, permits gradual release of excessive amounts of endolymph and thereby arrests the hydropic condition and Menière's attacks. However, man and knowledge are always in motion and some of Schuknecht's ideas do not bear closer examination.

BENIGN PAROXYSMAL POSITIONING VERTIGO (BPPV) AND VESTIBULAR NEURITIS, THE TWO MOST COMMON VESTIBULAR VERTIGO SYNDROMES

The common view that cupulolithiasis in BPPV simply reflects transformation of the affected cupula from a transducer of angular acceleration to one of linear acceleration secondary to the acquired specific gravity differential between the cupula fluid and endolymph, cannot be correct for several reasons: BPPV is a positioning rather than a positional vertigo and nystagmus; it is not induced by a particular head position relative to the gravitational vector but only by rapid changes in head position (Fig. 1); the paroxysmal nystagmus is compatible with a cupulogram of an ampullofugal stimulation of the posterior semicircular canal (angular acceleration causing inhibitory hair cell deflection, Fig. 2) rather than with ampullopetal positional effects (excitatory hair cell deflection) as expected by Schuknecht and others.

We believe that cupulolithiasis is mainly causative, in that the 'heavy cupula' creates

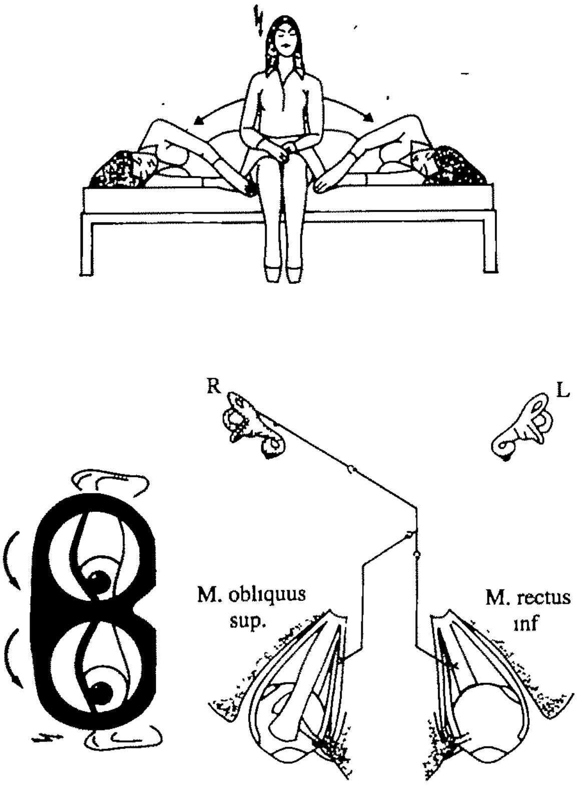

FIG. 1. Benign paroxysmal positioning vertigo and nystagmus are precipitated by rapid lateral head tilt towards the affected ear or by head extension (*top*). The typical nystagmus (best seen with Frenzel's glasses) beats towards the undermost ear rotating counter-clockwise with right ear lesions (*bottom, left*), and clockwise with left ear lesions. The rotary-linear nystagmus reflects ampullofugal stimulation of the posterior semicircular canal with activation of the ipsilateral superior oblique and contralateral inferior rectus eye muscles (*bottom right*).

an oversensitivity of the posterior canal to angular acceleration in the plane specific to the canal (Brandt, 1990). Thus, in a strict sense, BPPV constitutes an enhanced postrotatory positioning response but not a positional response. The intensity of positional nystagmus depends on the velocity of the positioning manoeuvre and BPPV attacks can be avoided if the challenging position is assumed very slowly.

The repeated clinical observation of the apparently paradoxical coincidence of BPPV and vestibular neuritis led to the suggestion that the three semicircular canals and the otoliths (utricle and saccule) may be separately involved in partial lesions (Büchele and Brandt, 1988). The coincidence of full vestibular neuritis and BPPV in the same individual, in the same ear, at the same time, seems impossible since it implies function and loss of function in one labyrinthine structure at the same time.

Vestibular neuritis affects only part of the vestibular nerve trunk, usually the superior division (horizontal semicircular canal paresis) which travels separately and has its own ganglion, whereas the inferior part (posterior semicircular canal) is spared. This hypothesis of partial involvement of the vestibular nerve (Fig. 3) is supported by the temporal bone pathology found by Schuknecht and Kitamura (1981) and also by the histopathology of a case of Herpes zoster oticus (Proctor *et al.*, 1979). In the latter case, the otolithic apparatus and the posterior semicircular canal remained intact.

Based on the mechanical hypothesis of cupulolithiasis, an effective physical therapy

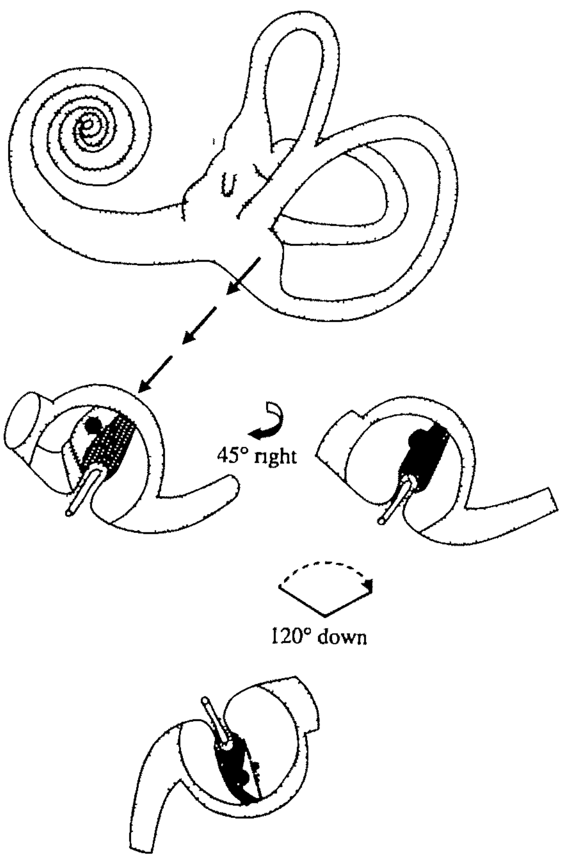

FIG. 2 Mechanism of cupulolithiasis, the most probable cause of benign paroxysmal positioning vertigo. Inorganic 'heavy particles', detached from the otoconial layer (by degeneration or head trauma) gravitate to and become settled on the cupula of the posterior semicircular canal. The 'heavy material' (filled circle) causes a specific gravity differential between cupula and endolymph with postrotatory overexcitability. After rapid head tilt towards the affected ear or after head extension, when the posterior semicircular canal is moved in the specific plane of stimulation, an ampullofugal deflection of the cupula occurs, with a rotational vertigo and concomitant nystagmus (Brandt, 1990).

for these patients was designed to promote the loosening and ultimative dispersion of the loose otolithic material from the cupula of the posterior canal (Brandt and Daroff, 1980*b*). Patients are instructed to systematically provoke vertigo attacks by repeatedly tilting their upper trunk and head into the challenging position (Fig. 1). The time course of individual recovery, fluctuating and with abrupt remissions, supports the recovery being due to a purely physical mechanism rather than central compensation by habituation.

There is a syndrome which can be best explained by transformation of the cupula from a transducer of angular to a transducer of linear acceleration. This is the *positional alcohol nystagmus and vertigo* syndrome (Bárány, 1911; Money *et al.*, 1974), the symptoms of which may perhaps not be totally unfamiliar from personal experience. The semicircular canals selectively transduce angular velocity and acceleration and under normal circumstances are insensitive to gravitational orientation and linear acceleration. If a considerable specific gravity differential occurs between cupula and endolymph then the semicircular canal should become sensitive to changes in head position within the gravitational field, resulting in positional rotatory vertigo and nystagmus (Fig. 4). This is called the Buoyancy hypothesis.

Alcohol is less dense than endolymph (Money *et al.*, 1974) and with increasing blood levels, alcohol diffuses into the cupula fluid rendering it less dense than endolymph.

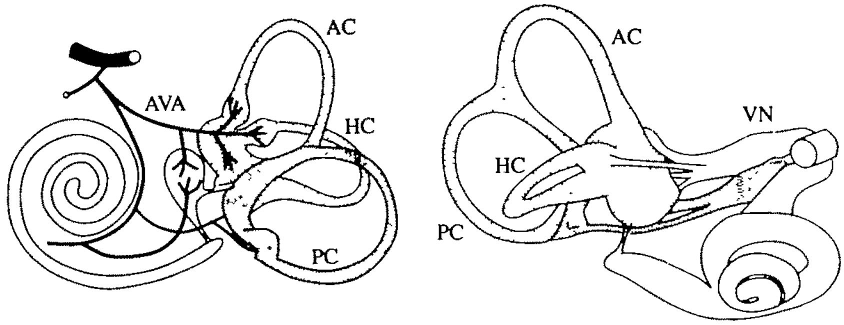

FIG. 3. Vestibular neuritis, a partial labyrinthine lesion with horizontal semicircular canal paresis: vascular or viral aetiology? Theoretical vascular explanation is that only the anterior vestibular artery (AVA) is affected, sparing the posterior branch which supplies the posterior canal (*top*). Possible viral aetiology of vestibular neuritis affecting parts of the nerve (VN) in particular horizontal ampollary nerve, but sparing the inferior division, the functioning of which is necessary for the occurrence of simultaneous vestibular neuritis and benign paroxysmal positioning nystagmus in the same ear. AC = anterior canal; HC = horizontal canal; PC = posterior canal.

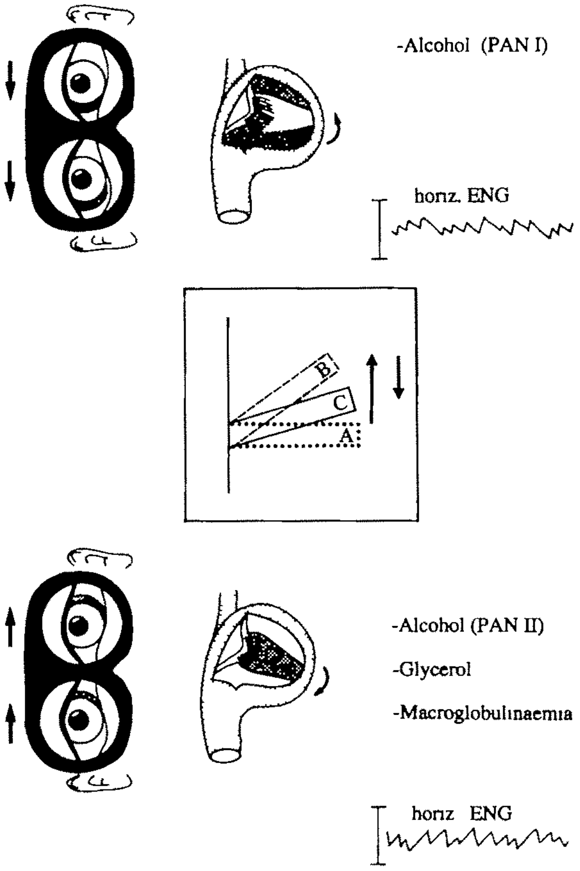

FIG. 4 Ingestion of water-soluble molecules with different specific gravities, such as alcohol, heavy water or glycerol, causes a specific gravity differential between cupula and endolymph (bouyancy hypothesis) with positional nystagmus and vertigo. During the resorption phase of alcohol, nystagmus beats towards the undermost ear (PAN I with the cupula relatively lighter than endolymph) Positional nystagmus beats towards the uppermost ear during alcohol-reduction phase (PAN II) as well as in glycerol-, heavy water-, and macroglobulinaemia-induced positional nystagmus (with the cupula relatively heavier than endolymph) The gravity-dependent deflection force on the cupula (insert, B) must be greater than the physiological restoring force (insert, C) for the positional nystagmus to last as long as the precipitating head position is maintained (Brandt, 1990).

During the resorption phase of alcohol, nystagmus beats towards the undermost ear when the subject lies down. With time, blood alcohol diffuses into the endolymph, equalizing its specific gravity with that of the cupula fluid. There is then a silent intermediate period beginning between 3.5 and 5 h after cessation of alcohol ingestion, when positional vertigo is absent. Alcohol selectively diffuses out of the cupula before it leaves the endolymph. This causes the cupula fluid to be transiently denser than the endolymph, thus initiating phase 2 of PAN, which begins between 5 and 10 h after cessation of drinking when there is a falling blood level. In PAN II, nystagmus beats to the uppermost ear. PAN II is usually associated with motion sickness and is a major contribution to the hangover. The 'morning after' drink of alcohol may indeed re-equalize the specific gravities and lessen, albeit transiently, the untoward symptoms (Brandt and Daroff, 1980*a*).

Peripheral vestibular disorders require collaboration between neurologists and their ear, nose and throat (ENT) colleagues. In clinical practice this is not always the case, and the unfortunate dizzy patient ends up in a kind of no-man's land between the two, each specialist believing that the other is the more appropriate for the patient's problem. The diagnosis of central vestibular malfunction is unequivocally the responsibility of the neurologist.

CLASSIFICATION OF VESTIBULAR BRAINSTEM DISORDERS ACCORDING TO VOR PLANES

It is well recognized that some of the supranuclear ocular motor disorders are secondary to distinct and separated lesions of central vestibular pathways from the vestibular nuclei to ocular motor nuclei. A classification of central vestibular disorders of the brainstem and vestibulo-cerebellum does not exist. Therefore an attempt will be made to attribute downbeat/upbeat nystagmus, pseudo-vestibular neuritis and ocular tilt reaction to lesional tone imbalances in any one of the three major planes of action of the vestibulo-ocular reflex.

The three-dimensional vestibulo-ocular reflex (VOR)

The VOR normally serves to hold the direction of gaze in space constant during head movements by forcing the eyes to move in their orbits in the direction opposite to that of head motion with a velocity and amplitude, which 'compensates' for the head motion. The VOR has three major planes of action: (1) horizontal head rotation about a vertical z-axis = yaw; (2) head extension and flexion about horizontal y-axis = pitch; and (3) lateral head tilt about horizontal x-axis = roll. These planes represent three-dimensional space in the vestibular and oculomotor system with different demands upon the VOR for perception of a stable world and postural balance during head rotations in yaw, pitch or roll.

The neuronal network mediating VOR of horizontal and vertical semicircular canals is based upon sensory convergence within a three-neuron reflex arc. It links a set of extraocular muscles with their primary action roughly aligned to the particular spatial plane of either the horizontal, the anterior or posterior canal. Sensory-motor transformation from canal planes to the planes of eye movements has been demonstrated at the level of second-order neurons within the vestibular nuclei (Graf and Ezure, 1986).

When the head is turned all semicircular canals are stimulated. However, VOR in yaw is predominantly mediated by the horizontal canals. VOR in pitch and roll is predominantly mediated by the vertical anterior and posterior canals. Spatial organization of right and left labyrinths in temporal bones is such that horizontal and vertical canals can be paired with respect to their optimal plane of function although the canals are not completely coplanar.

It is not correct to say that the VOR merely serves stabilization of gaze. Its neuronal pathways also include ascending input to the thalamo-cortical projections of perception as well as descending input to vestibulo-spinal projections for adjustments of head and body posture (vestibulo-spinal reflexes). This means that both physiological stimulation and pathological dysfunction of the semicircular canal input, not only provoke nystagmus but inevitably cause a direction specific concurrent rotary vertigo and postural imbalance.

Brainstem disorders of the VOR

Evidence can be presented for a reasonable classification of some central vestibular syndromes of the brainstem tegmentum (*see* Table 1).

Pseudo-vestibular neuritis

Frequent vestibular neuritis is caused by viral infection of the vestibular nerve and is most probably a partial rather than a complete vestibular paresis with predominant involvement of the horizontal semicircular canal (Büchele and Brandt, 1988). Small infarctions in the territory of either the anterior inferior cerebellar artery (AICA) or the posterior inferior cerebellar artery (PICA) have been repeatedly reported to mimic unilateral peripheral labyrinthine disorder, mostly with a similarly benign course (Duncan *et al.*, 1975; Rubenstein *et al.*, 1980). Hopf (1987) described cases with additional impairment of the masseter reflex and argued that a small region ventro-lateral to the floor of the fourth ventricle can be the causative area because structures serving both vestibular and trigeminal motor function are present in this area. A demyelinating plaque in multiple sclerosis may also mimic signs of vestibular neuritis, including caloric hyporesponsiveness, if it is located at the root entry zone of the eighth nerve (Brandt *et al.*, 1986). These brainstem disorders may involve more than the horizontal semicircular canal pathways and one can easily find cases that confound this classification scheme.

Downbeat nystagmus/vertigo

Downbeat nystagmus in the primary position of gaze, accompanied by oscillopsia and postural instability, is a clearly defined syndrome almost specific to structural lesions of the paramedian craniocervical junction. It is due to a tone imbalance of the vertical

TABLE 1 CLASSIFICATION OF SOME CENTRAL VESTIBULAR SYNDROMES OF THE BRAINSTEM TEGMENTUM

Disorders of the VOR in horizontal (yaw) plane	Horizontal nystagmus, pseudo 'vestibular neuritis' (partial AICA/PICA infarctions; MS-plaques)
Disorders of the VOR in sagittal (pitch) plane	Downbeat nystagmus/vertigo, upbeat nystagmus/vertigo
Disorders of the VOR in frontal (roll) plane	Ocular tilt reaction (skew deviation; cyclorotation of the eyes; body lateropulsion)

semicircular canal reflexes in the pitch plane. Structural lesions involve either the floor of the fourth ventricle between the vestibular nuclei, which interrupts the tonic excitatory activity to the inferior recti muscles or a bilateral lesion of the flocculus, which leads to an increase in tonic excitatory input to the superior recti muscles due to a disinhibition (De Jong *et al.*, 1980; Baloh and Spooner, 1981; Zee *et al.*, 1981).

Upbeat nystagmus/vertigo

Upbeating nystagmus in the primary position of gaze, with concomitant oscillopsia and postural imbalance, is a pendant of downbeat nystagmus (towards the opposite direction) and also reflects a tone imbalance of vertical VOR in pitch (Fig. 5). Two separate intra-axial brainstem lesions in the tegmentum of the ponto-mesencephalic and the ponto-medullary junction, near the perihypoglossal nuclei, are likely to be responsible for this syndrome (Fisher *et al.*, 1983). There is also speculation about the functional significance of a ventral tegmental pathway (Ranalli and Sharpe, 1988), a lesion of which causes the syndrome.

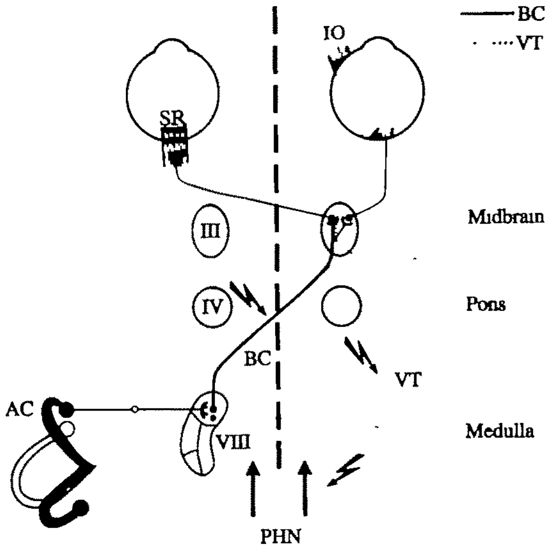

FIG. 5. Schematic representation of three-neuron excitatory reflex arc from the anterior semicircular canal (AC), the superior vestibular nucleus (VIII), the brachium conjunctivum (BC) to the contralateral oculomotor nucleus (III) the superior rectus muscle (SR) and inferior oblique muscle (IO) Also shown is the excitatory ventral tegmental pathway (VT), which connects the superior vestibular nucleus with the contralateral oculomotor nucleus. An ascending pathway from the perihypoglossal nuclei (PHN) in the medulla possibly modulates the tone of the vertical VOR. The arrows indicate the lesions of the brachium conjunctivum, the ventral tegmental pathway, and the perihypoglossal connection, which may produce upbeat nystagmus.

Ocular tilt reaction (OTR)

This eye-head synkinesis consists of lateral head tilt, skew deviation of the eyes (hypotropia of the undermost eye) and cyclorotation as first clearly delineated by electrical stimulation of the rostral midbrain tegmentum of the monkey (Westheimer and Blair, 1975). It represents a fundamental pattern of coordinated eye-head roll motion based upon both utricular and vertical canal input (Brandt and Dieterich, 1987). In clinical cases of OTR, structural or functional lesions involve graviceptive pathways and the pathways for the VOR in roll from the medulla (Brandt and Dieterich, 1987) to meso-diencephalon (Halmagyi *et al.*, 1990). VOR in roll is mediated by the vertical anterior and posterior canals (Figs 5, 6). With sustained head tilt, the otoliths contribute in that static otolith reflexes partially compensate for eye position in roll (ocular counter-rolling).

This classification of central vestibular disorders according to VOR planes in its present form is speculative since it combines semicircular canal and otolith function. It is incomplete since other vestibular syndromes such as infratentorial central-positional nystagmus/vertigo, familial periodic vertigo, paroxysmal vertigo evoked by lateral gaze or supratentorial syndromes such a thalamic astasia and vestibular epilepsy are not included (Brandt, 1991). *See* Table 2.

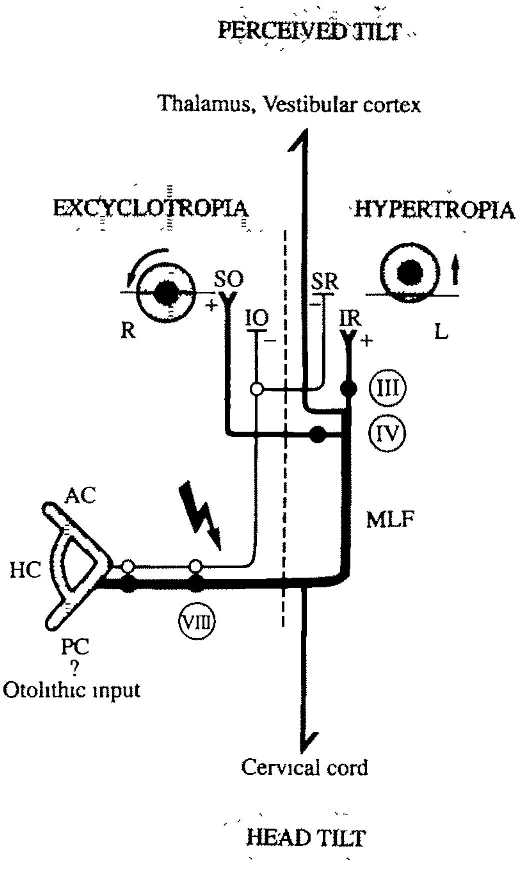

FIG. 6. Hypothetical explanation of OTR in Wallenberg's syndrome (Brandt and Dieterich, 1987). Schematic representation of the three-neuron vestibulo-ocular reflex arc between posterior semicircular canal and extraocular eye muscles. It probably also conveys otolith information An excitatory ascending pathway is linked to the ipsilateral superior oblique and the contralateral inferior rectus; an inhibitory ascending pathway is linked to ipsilateral inferior oblique and contralateral superior rectus (Graf and Ezure, 1986) A lesion of these pathways near the vestibular nuclei complex causes excyclotropia of the ipsilateral and hypertropia of the contralateral eye This pattern reflects oculomotor abnormality of OTR in Wallenberg's syndrome Concurrent deviation of subjective visual vertical as well as head tilt could be mediated by ascending perceptual pathways to the vestibular cortex and descending vestibulo-spinal pathways to the upper cervical cord, respectively HC, AC, PC, horizontal, anterior and posterior semicircular canals, MLF, medial longitudinal fasciculus, SO, IO, superior and inferior oblique muscles, SR, IR, superior and inferior rectus muscles

WHY ARE OTOLITH DISORDERS MISSING FROM THE DIAGNOSTIC REPERTOIRE OF NEUROLOGISTS?

The answer is that we do not have reliable clinical tests of otolith function. I am convinced that there are a number of peripheral and central disorders of otolith function which we will be able to recognize in the near future.

'Man in motion' causes space sickness in microgravity, a major restraint on space craft missions. Active head movements do not elicit motion sickness within gravitational

TABLE 2 CENTRAL VESTIBULAR VERTIGO SYNDROMES

Site	*Syndrome*	*Mechanism/Aetiology*
Vestibular cortex	Vestibular epilepsy	Simple partial seizures
Thalamus (interstitial nucleus of Cajal)	Ocular tilt reaction	Paramedian thalamic infarction, haemorrhage
	Thalamic astasia	Posturolateral thalamic lesions
Vestibulocerebellum		
Flocculus	Downbeat nystagmus/vertigo	Disinhibition of vertical VOR in pitch
Nodulus	Positional downbeat nystagmus	Inappropriate otolith—canal interaction?
Vestibular nuclei, vestibulocerebellar loop?	Central positional vertigo and/or nystagmus	Inappropriate otolith—canal interaction?
Mesodiencephalic brainstem	Ocular tilt reaction	Tone imbalance of VOR in roll
	Upbeat nystagmus/vertigo	Tone imbalance of vertical VOR in pitch
Pontomedullary brainstem	Paroxysmal dysarthria/ataxia in MS	Transversally spreading ephaptic axonal activation
	Pseudo 'vestibular neuritis'	Vestibular nerve root plaque in MS or lacunar infarction
	Ocular tilt reaction	Graviceptive pathway lesion with tone imbalance of VOR in roll
	Downbeat nystagmus/vertigo	Tone imbalance of VOR in pitch
Medullary brainstem	Upbeat nystagmus/vertigo	Tone imbalance of VOR in pitch
	Paroxysmal vertigo evoked by lateral gaze or head position	Vestibular nuclei lesion?
Brainstem and cerebellum	Pseudo 'vestibular neuritis'	Ischaemia of superior labyrinth, vestibular nerve, vestibular nuclei (AICA or PICA infarction)
	Lateropulsion in Wallenberg's syndrome	Ischaemic lesion-induced deviation of subjective vertical
	Familial periodic vertigo	Hereditary, metabolic?
	Encephalitis with predominant vertigo	Virus infection
	Epidemic vertigo	Virus infection

conditions on earth but do so in weightlessness. In the early Gemini and Mercury space craft programs, astronauts were restrained in their seats and did not develop symptoms, thus indicating that a factor other than microgravity was involved. In subsequent Apollo and Skylab missions, the astronauts were free to move. A close relationship between dizziness and active head movements was observed (Graybiel *et al.*, 1977).

Two explanations have been suggested for space sickness. One is that the symptoms are generated by an intravestibular mismatch between the otoliths and the semicircular canals as raised by Benson (1977). A second possible mechanism for space sickness is related to the normal slight difference in absolute weights of the two otoliths as suggested by von Baumgarten and Thümler (1979). This biological difference is compensated for by central mechanisms in the gravitational environment on earth. In the microgravity of space, a recalibration is required and astronauts are symptomatic until it is accomplished.

The latter explanation sounds reasonable and is supported by clinical observations in patients with newly acquired BPPV. During the initial course of the disease, patients may also complain of other symptoms of otolithic vertigo, especially a head motion intolerance with oscillopsia and the somatosensory sensation of walking on pillows. This sensation probably arises from unequal excess loading of the two utricular otoliths, when parts of it are dislodged.

The majority of cases of dizziness and disequilibrium following head trauma may be due to otolith trauma. Otoconia are easily dislodged by linear accelerations or centrifuging in animals. The calcareous material embedded in the matrix may loosen, resulting in unequal loads on the macula beds and a tonus imbalance between the two otoliths. Engineering accelerometers are similarly vulnerable. Patients often describe their post-traumatic vertigo as a non-rotatory to-and-fro vertigo which is particularly associated with head acceleration and an unsteadiness in gait. Since the post-traumatic symptoms resemble otolith dysfunction in many patients one might speculate that this vulnerable accelerometer is affected by trauma. Central compensation would account for the gradual recovery within days or weeks, supporting the view that exercise is the best therapy for vertigo.

Recently, we were able to study an otolith disorder in a patient with an *otolithic Tullio phenomenon* (Brandt *et al.*, 1988; Dieterich *et al.*, 1989) who has sound-induced vestibular symptoms such as vertigo, nystagmus, oscillopsia and postural imbalance in perilymph fistulas. This patient, a professional horn player, complained about distressing attacks of oscillopsia as well as postural imbalance elicited by loud sounds particularly when applied to the left ear with a maximum at a frequency of 500 Hz. Surgical exploration of the middle ear revealed a subluxated stapes footplate with the hypertrophic stapedius muscle causing pathologically large amplitude movements during the stapedius reflex, pushing the otoliths (Fig. 7).

Objectively, simultaneous paroxysms of eye-head synkinesis (OTR) could be observed with the triad of skew deviation, ocular torsion and head tilt (Fig. 8). The latency of the eye movements was 22 ms, a unique measure of the (otolith) VOR latency in man.

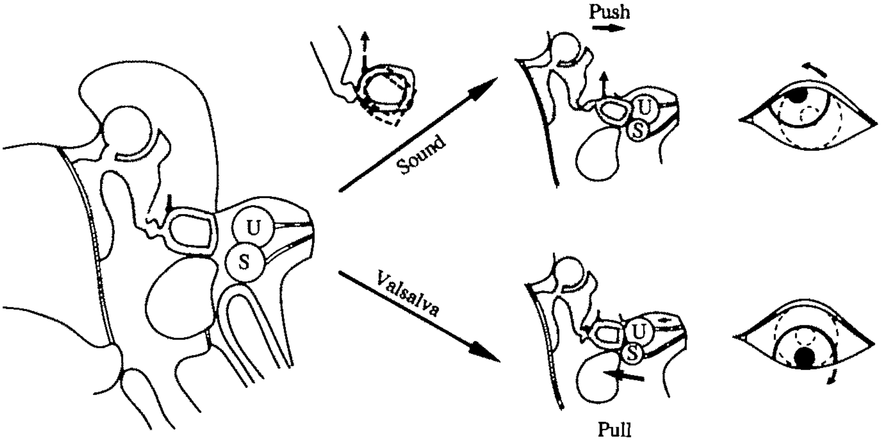

FIG. 7. Schematic drawing of the push and pull mechanism of the otoliths involved by the tilting of the stapes footplate, induced either by the stapedius reflex (push) or the Valsalva manoeuvre (pull) in an otolith Tullio phenomenon. In the latter condition increased intracranial pressure is transmitted towards the middle ear. Direction of induced eye movements are opposite, either up or down, indicative for the mode of stimulation (Dieterich *et al.*, 1989).

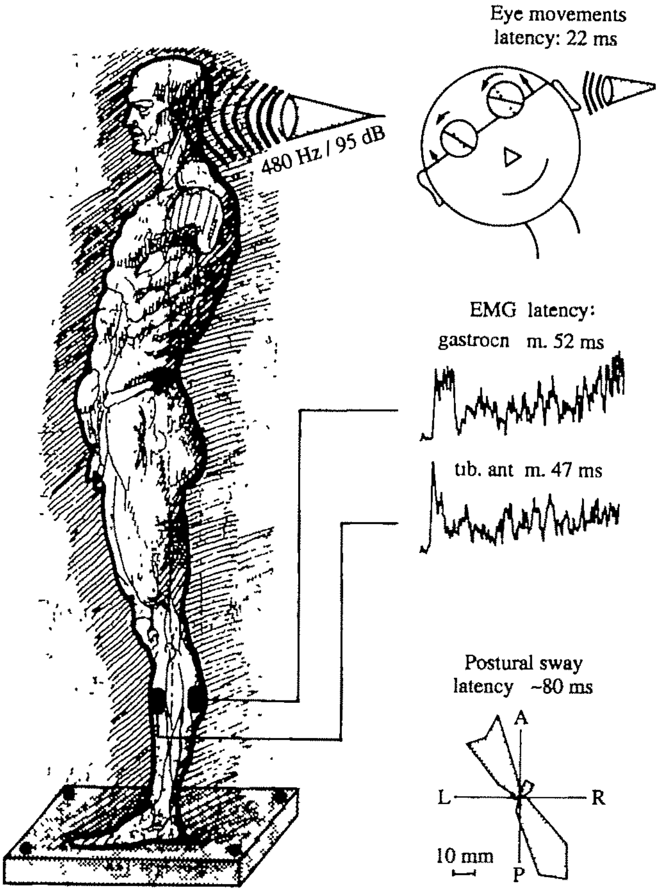

FIG. 8 An otolith Tullio phenomenon (*left*) is characterized by a sound-induced ocular tilt reaction (skew deviation with ipsilateral over contralateral hypertropia, ocular torsion counterclockwise and head tilt with ipsilateral ear up (*top*) and increased body sway predominantly from right-backward to left-forward (*bottom*). Latencies of disconjugated eye movements were 22 ms for the left eye, latencies of the vestibulo-spinal reflex at upright stance were 47 ms in the left tibialis anterior muscle and 52 ms in the left gastrocnemius muscle (*centre*). Measurable postural sway had a minimal latency of about 80 ms (*bottom*) (Brandt *et al.*, 1988)

Latencies for the vestibulo-spinal reflex during upright stance were 47 ms in the left tibialis anterior muscle and 52 ms in the left gastrocnemius muscle. This sound-induced paroxysmal ocular tilt reaction permits otolith reflex studies which hitherto were not possible in healthy subjects. The functional role of the otoliths in counteracting rapid pertubations of the body in order to maintain postural balance is still a matter of controversy. The strong EMG response in our patient, 47 ms at the earliest, causing a measurable body sway after 80 ms, strongly suggests the important function of vestibulo-spinal reactions transduced by the otoliths. Calculations taking into account the delay of the stapedius reflex of 5 – 10 ms suggest that the reflex arc from the utricular macula to the effector muscle is based on a three-neuron arc. This finding is in contrast to earlier views of others. It was argued by Nashner (1976), as well as Dietz and Berger (1982), that the otolith response is too late to counterbalance pertubation because the vestibular system initiates muscle response only after some 180 ms.

VISUAL-VESTIBULAR INTERACTION

When talking about the vestibular system one should never forget the visual and the somatosensory system. These three sensory systems subserve both static and dynamic spatial orientation, eye movements, locomotion and control of posture, by constantly providing reafferent cues. It is the sensory mismatch rather than the sensory loss which causes vertigo. When information from two sensory sources conflict, the intensity of the vertigo is a function of the degree of mismatch.

Visual vertigo the symptoms of which may include spatial disorientation, apparent motion (oscillopsia), postural imbalance and nausea is either induced by unusual visual stimulation (height vertigo) or ocular motor disorders causing a dissociation of visual and somatosensory straight ahead (Brandt, 1991; Fig. 9).

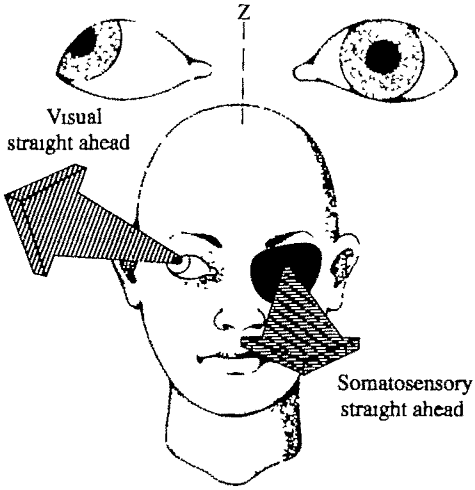

FIG 9. Visual vertigo: dissociation of subjective visual and somatosensory straight ahead (monocular) vision in a patient suffering from an acute extra-ocular muscle paresis with deviation of normal eye position due to myasthenia gravis (Brandt, 1991)

The term 'non-vestibular vertigo syndromes' refer to visual and somatosensory vertigo. In a strict sense such a distinction is not correct, because convergence of multisensory inputs at various levels of the central vestibular system sometimes makes it impossible for neurons as well as for conscious perception to differentiate clearly between vestibular somatosensory and visual stimulation (Dichgans and Brandt, 1978).

In 1794 *Erasmus Darwin*, the grandfather of Charles Darwin, wrote concerning visual vertigo in his zoonomia, or the laws of organic life: 'many people, when they arrive at 50 or 60 yrs of age, are affected with slight vertigo; which is generally but wrongly ascribed to indigestion, but in reality arises from a beginning defect of their sight . . . these people do not see objects so distinctly as formerly, and by exerting their eyes more than usual they perceive the apparent motions of objects, and confound them with the real motions of them; and therefore cannot accurately balance themselves so as easily to preserve their perpendicularity by them'. It is remarkable, historically, that this description of visual vertigo and its consequences for postural balance dates back to a time at which vestibular function was not yet understood, nearly a century before Mach's (1875) *Fundamentals of the Theory of Motion Perception.*

As we are in England recalling Darwin and visual vertigo, how could one better continue our historical survey than by stressing the merits of *Gordon Holmes*, the great scientist and neurologist. He advanced our understanding of visual orientation, stereopsis, eye movements and ocular palsies. His interest in dynamic spatial orientation was mainly visual and oculomotor. A typical title of one of his late lectures was: 'Looking and seeing: movements and fixation of the eyes', given as the John Mallet Purser Lecture in 1936. I cannot do better than to end with the closing words which he used on that occasion: 'The subject of this lecture is, therefore, of great significance in the ordinary routine of life, and an inquiry into its nature and into the factors which control it, will I hope justify my incursion into physiology, even though I have been able to approach it only from the restricted field of clinical pathology.'

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REFERENCES

BALOH RW, SPOONER JW (1981) Downbeat nystagmus: a type of central vestibular nystagmus. *Neurology, New York,* **31,** 304–310

BÁRÁNY R (1911) Experimentelle Alkoholintoxikation. *Monatsschrift für Ohrenheilkunde,* **45,** 959–962.

BÁRÁNY R (1921) Diagnose von Krankheitserscheinungen im Bereiche des Otolithenapparates. *Acta Otolaryngologica, Stockholm,* **2,** 434–437.

BAUMGARTEN VON RJ, THUMLER R (1979) A model for vestibular function in altered gravitational states. In: *Life Sciences and Space Research.* Edited by R. Holmqvist Oxford: Pergamon Press, pp. 161–170

BENSON AJ (1977) Possible mechanisms of motion and space sickness. *Proceedings of the European Symposium on Life Sciences Reseach in Space* European Space Agency Sp-130, 101–108.

BRANDT TH (1990) Positional and positioning vertigo and nystagmus *Journal of the Neurological Sciences,* **95,** 3–28.

BRANDT TH (1991) *Vertigo: Its Multisensory Syndromes.* London: Springer.

BRANDT TH, DAROFF RB (1980*a*) The multisensory physiological and pathological vertigo syndromes. *Annals of Neurology,* **7,** 195–203.

BRANDT TH, DAROFF RB (1980*b*) Physical therapy for benign paroxysmal positional vertigo. *Archives of Otolaryngology,* **106,** 484–485.

BRANDT TH, DIETERICH M, BUCHELE W (1986) Postural abnormalities in central vestibular brain stem lesions. In: *Disorders of Posture and Gait.* Edited by W. Bles and Th. Brandt. Amsterdam. Elsevier, pp. 141–156.

BRANDT TH, DIETERICH M (1987) Pathological eye-head coordination in roll: tonic ocular tilt reaction in mesensephalic and medullary lesions. *Brain,* **110,** 649–666.

MBRANDT TH, DIETERICH M, FRIES E (1988) Otolithic Tullio phenomenon typically presents as paroxysmal ocular tilt reaction. *Advances in Oto-Rhino-Laryngology,* **42,** 153–156

BUCHELE W, BRANDT TH (1988) Vestibular neuritis—a horizontal semicircular canal paresis? *Advances in Oto-Rhino-Laryngology,* **42,** 157–161.

COHEN B (1984*a*) The roots of vestibular and oculomotor research Introduction. *Human Neurobiology,* **3,** 121.

COHEN B (1984*b*) Erasmus Darwin's observations on rotation and vertigo. *Human Neurobiology,* **3,** 121–128.

CRUM-BROWN A (1874) On the sense of rotation and the anatomy and physiology of the semicircular canals of the internal ear. *Journal of Anatomy and Physiology,* **8,** 327–331.

De Jong JMBV, Cohen B, Matsuo V, Uemura T (1980) Midsagittal pontomedullary brain stem section: effects on ocular adduction and nystagmus. *Experimental Neurology*, **68**, 420–442.

Dichgans J, Brandt Th (1978) Visual-vestibular interaction: effects on self-motion perception and postural control. In: *Handbook of Sensory Physiology*, Volume 8: *Perception*. Edited by R. Held, H. W. Leibowitz and H.-L. Teuber. Berlin: Springer, pp. 755–804

Dieterich M, Brandt Th, Fries W (1989) Otolith function in man: results from a case of otolith Tullio phenomenon. *Brain*, **112**, 1377–1392.

Dietz V, Berger W (1982) Spinal coordination of bilateral leg muscle activity during balancing. *Experimental Brain Research*, **47**, 172–176.

Duncan GW, Parker SW, Fisher CM (1975) Acute cerebellar infarction in the PICA territory. *Archives of Neurology, Chicago*, **32**, 364–368.

Fisher A, Gresty M, Chambers B, Rudge P (1983) Primary position upbeating nystagmus· a variety of central positional nystagmus. *Brain*, **106**, 949–964.

Graf W, Ezure K (1986) Morphology of vertical canal related second order vestibular neurons in the cat. *Experimental Brain Research*, **63**, 35–48.

Graybiel A, Miller EF, Homick JL (1977) Experiment M 131: human vestibular function. In: *Biomedical Results from Skylab*, NASA Sp 377, Washington, DC, 74–103.

Grüsser O-J (1984) J. E. Purkyne's contributions to the physiology of the visual, the vestibular and the oculomotor systems. *Human Neurobiology*, **3**, 129–144.

Hallpike CS (1949) The pathology and differential diagnosis of aural vertigo. *Proceedings of the 4th International Congress of Otolaryngology*, British Medical Association 2, 514.

Halmagyi GM, Brandt Th, Dieterich M, Curthoys IS, Stark RJ, Hoyt WF (1990) Tonic contraversive ocular tilt reaction due to unilateral meso-diencephalic lesion. *Neurology, Cleveland*, **40**, 1503–1509.

Henn V (1984) E Mach on the analysis of motion sensation. *Human Neurobiology*, **3**, 145–148.

Henn V, Young LR (1975) Ernst Mach on the vestibular organ 100 years ago. *ORL. Journal of Otorhinolaryngology and its Related Specialities*, **37**, 138–148.

Hopf HC (1987) Vertigo and masseter paresis. A new local brainstem syndrome probably of vascular origin. *Journal of Neurology*, **235**, 42–45.

Mach E (1875) *Grundlinien der Lehre von den Bewegungsempfindungen*. Leipzig· Engelmann.

Menière PC (1861) Mémoire sur les lésions de l'oreille interne dominant lieu à des symptomes de congestion cérébrale apoplectiforme. *Gazette Médicale de Paris*, Sér 3, **16**, 597–601.

Money KE, Myles WS, Hoffert BM (1974) The mechanism of positional alcohol nystagmus. *Canadian Journal of Otolaryngology*, **3**, 302–313.

Nashner LM (1976) Adapting reflexes controlling the human posture. *Experimental Brain Research*, **26**, 59–72.

Proctor L, Perlman H, Lindsay J, Matz G (1979) Acute vestibular paralysis in herpes zoster oticus. *Annals of Otology, Rhinology and Laryngology*, **88**, 303–310.

Ranalli RJ, Sharpe JA (1988) Upbeat nystagmus and the ventral tegmental pathway of the upward vestibulo-ocular reflex. *Neurology, Cleveland*, **38**, 1329–1330.

Rubenstein RL, Norman DM, Schindler RA, Kaseff L (1980) Cerebellar infarction—a presentation of vertigo. *Laryngoscope*, **90**, 505–514.

Ruttin B (1909) Zur Differentialdiagnose der Labyrinth- und Hörnerberkrankungen. *Zeitschrift fur Ohrenheilkunde*, **57**, 327–331.

Schuknecht HF (1969) Cupulolithiasis. *Archives of Otolaryngology*, **90**, 765–768.

Schuknecht HF, Ruby RRF (1973) Cupulolithiasis. *Advances in Oto-Rhino-Laryngology*, **20**, 434–443.

Schuknecht HF, Kitamura K (1981) Vestibular neuritis. *Annals of Otology, Rhinology and Laryngology*, **90**, Supplement 78, 1–19.

Schuknecht HF, Gulya AJ (1983) Endolymphatic hydrops: an overview and classification. *Annals of Otology, Rhinology and Laryngology*, **92**, Supplement 106, 1–20.

Westheimer G, Blair SM (1975) The ocular tilt reaction—a brainstem oculomotor routine. *Investigative Ophthalmology*, **14**, 833–839.

Zee DS, Yamazaki A, Butler PH, Guçer G (1981) Effects of ablation of flocculus and paraflocculus on eye movements in primate. *Journal of Neurophysiology*, **46**, 878–899.

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VASCULITIC NEUROPATHY

A CLINICAL AND PATHOLOGICAL STUDY

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SUMMARY

The clinical, electrophysiological and pathological features and prognosis of 34 patients with peripheral neuropathy caused by necrotizing vasculitis were evaluated. The causes included polyarteritis nodosa and its Churg-Strauss variant, rheumatoid arthritis, undifferentiated connective tissue disease, Wegener's granulomatosis, primary Sjögren's disease, and chronic lymphocytic leukaemia with cryoglobulinaemia; 2 patients had no evidence of systemic vasculitis. Mononeuritis multiplex was the most common clinical manifestation, followed by asymmetrical polyneuropathy and distal symmetrical polyneuropathy. Pain was a frequent symptom. Nerve conduction studies were abnormal in all cases, and in 3 patients there was conduction block or severe slowing of motor conduction. Necrotizing vasculitis was present in sural nerve biopsies of most cases, and severe active axonal degeneration was a dominant feature. Immunofluorescent staining of blood vessels for immunoglobulin, C_3 and fibrinogen was positive in all cases in which it was performed, even when there was no cellular infiltration.

All patients were treated with prednisone alone or in combination with other immunosuppressive agents, or with plasmapheresis. Long-term follow-up studies demonstrated that although the peripheral neuropathy usually improved and caused only mild to moderate functional disability, the long-term prognosis of the systemic disease was poor with a 5-yr survival of only 37%.

INTRODUCTION

The term vasculitis indicates inflammation and necrosis of blood vessel walls leading to luminal narrowing and distal ischaemia; multiple or isolated organ systems may be involved in the vasculitic process that is presumed to be immunologically mediated. Vasculitic diseases have been classified pathologically according to the size of the blood vessel wall involved (Zeek, 1952), as well as in clinical terms (Fauci *et al.*, 1978), but it is difficult to classify patients with systemic vasculitic neuropathy into exact disease categories (Kissel *et al.*, 1985; Harati and Niakan, 1986).

Peripheral nervous system involvement is common in systemic vasculitis occurring most frequently in the polyarteritis nodosa (PAN) group of disorders (Moore and Cupps, 1983; Guillevin *et al.*, 1988) and in rheumatoid vasculitis (Scott *et al.*, 1981). Although large follow-up studies of patients with PAN and rheumatoid vasculitis have been reported (Frohnert and Sheps, 1967; Sack *et al.*, 1975; Cohen *et al.*, 1980; Scott *et al.*, 1981), there have been few studies of the prognosis of vasculitic neuropathy. Chang *et al.* (1984) focused attention on patients with mononeuritis multiplex and Dyck *et al.* (1987) on those without systemic manifestations. The present study was undertaken to examine

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the clinical and pathological features of 34 patients with peripheral neuropathy caused by vasculitis and to determine the prognosis of this group based on a follow-up study of their clinical condition.

METHODS

Patient selection and follow-up

1024 nerve biopsies performed in our department from 1974 to 1986 were analysed. Seven patients with systemic lupus erythematosus previously reported (McCombe *et al.*, 1987) were excluded from further analysis. Thirty-four patients were considered on review of the pathology to have unequivocal necrotizing vasculitis based on blood vessel morphology (30 nerve biopsies, 2 muscle biopsies, 1 renal biopsy and 1 autopsy). Other causes of peripheral neuropathy were excluded by history, physical examination and appropriate laboratory tests. The case records were reviewed and follow-up information obtained in all 34 patients included in the final analysis; living patients were reviewed clinically and their disability graded on a functional scale (Prineas, 1970).

Clinical data and patient classification

Clinical and electrophysiological data were obtained from case records and then analysed. The type of collagen vascular disease was classified wherever possible, according to standard criteria, as polyarteritis nodosa or its Churg-Strauss variant, rheumatoid vasculitis, primary Sjögren's disease or vasculitis associated with Wegener's granulomatosis or cryoglobulinaemia (Fauci *et al.*, 1978; Rodnan *et al.*, 1983). Patients having several clinical and laboratory indicators of collagen vascular disease but in whom no definitive diagnosis had been made were classified as having undifferentiated connective tissue disease. Patients with no clinical evidence of a disorder affecting more than the peripheral nervous system were classified as having isolated peripheral nervous system involvement. Neuropathies were classified as mononeuritis multiplex, asymmetrical neuropathy or distal symmetrical sensorimotor neuropathy on clinical grounds alone. Nerve conduction studies were performed using standard techniques.

Since the diagnosis of vasculitic neuropathy was made by sural nerve biopsy, the date of this procedure was taken as the time of diagnosis for the purposes of data analysis.

Histological techniques

The techniques have been fully described elsewhere (Walsh and McLeod, 1970; Low *et al.*, 1978). Whole sural nerve biopsy was performed at the level of the lateral malleolus under local anaesthesia. The nerve was divided into 3–5 portions, each about 1 cm in length. One piece of each nerve was fixed in picric acid, embedded in paraffin and cut transversely and longitudinally in sections of 5 μm thickness. The sections were stained with haematoxylin and eosin (H and E). Another piece was stained for 24 h in 1% osmium tetroxide, macerated in glycerol and teased apart under a dissecting microscope in order to isolate single nerve fibres. One piece was fixed in cold 3% glutaraldehyde in 0.1 M cacodylate buffer for 3 h followed by 2% osmium tetroxide for 1 h. The tissue was dehydrated in graded concentrations of ethanol, embedded in Spurr's resin and cut transversely in 0.5–1.0 μm sections that were stained with toluidine blue. Another portion of nerve was frozen in liquid nitrogen and from this portion cryostat sections were cut for immunohistochemical staining. Photomicrographs of plastic embedded, toluidine blue-stained sections of fascicles selected according to methods described by Dyck *et al.* (1979) were printed on photographic paper at an enlargement of ×1100. The number of fibres not undergoing active degeneration was counted and their external diameters measured with a Zeiss TGZ3 particle-size analyser set in the linear mode. The diameter of the light spot was adjusted to approximate to the mean diameter of each fibre. The endoneurial area of the fascicles was measured with a digitizer attachment (HP9864A) of a Hewlett-Packard 9815A programmable calculator. The fibre density was calculated as the number of fibres/mm^2 of intraperineurial area. Histograms of fibre diameter distribution were drawn with a plotter (HP9862A).

Immunofluorescence

A section of sural nerve removed at biopsy was snap frozen and stored in liquid nitrogen. 5 μm cryostat sections of nerve were air dried and fixed in acetone for 10 min. Fluorescein isothiocyanate (FITC) conjugated sheep antihuman immunoglobulin was applied to the sections for 45 min. The antibodies used were antihuman immunoglobulin (G, M and A) antihuman IgG, antihuman IgM, antihuman IgA, and antibodies to the third component of complement (C_3) and to fibrinogen. These conjugated antibodies (Wellcome Laboratories) were diluted 1:10 in phosphate buffered saline (PBS). After incubation, the sections were drained and washed twice in PBS for 15 min each and then mounted with 10% glycerol in PBS and examined immediately under a Zeiss fluorescent microscope.

Classification of nerve pathology

Affected neural blood vessels were assessed with regard to (1) *location*: epineurial, perineurial, endoneurial; (2) *size*: the smallest diameter measured at the outer layer of the media; (3) *necrosis of the vessel wall*; (4) *inflammatory reaction* in or around the vessel with neutrophils, lymphocytes, plasma cells, macrophages or eosinophils. The cellular reaction was classed as mild, moderate, or severe; (5) *healing* as assessed by focal or circumferential fibrosis of the vessel wall or focal loss of the internal elastic lamina

The presence of necrotizing vasculitis in nerve biopsies was judged to be (1) *definite (D)* if there was either (a) vessel wall necrosis and an inflammatory reaction, or (b) evidence of healing; (2) *probable (P)* if an inflammatory reaction was seen in or around a vessel with a diameter greater than 30 μm; (3) *absent (A)* if none of the above, or only non-specific such as intimal proliferation, were present.

Statistical analysis

A Cox regression analysis (Cox and Oakes, 1984) was used to study prognostic factors for survival. A backward selection procedure was used to find the simplest significant model. A secondary analysis studied the actual and expected survival of the group Actual survival was calculated using a Kaplan-Meier survival plot (Cox and Oakes, 1984) and the relative survival calculated using life table methods based on age and sex data from Australian mortality tables (Australian Life Tables 1980–1982).

RESULTS

Pathological features

Blood vessels. Using the above criteria 30 patients had nerve biopsy evidence of definite vasculitis (Table 1). Three patients were classified as probable vasculitis; they had definite necrotizing vasculitis in other tissue (2 muscle biopsies, 1 renal biopsy). One case in which the nerve biopsy did not have the features of vasculitis (classified as absent), but who had widespread necrotizing vasculitis at autopsy, was included in the statistical analysis. Of 57 affected blood vessels, 52 were located in the epineurium, 3 in the perineurium, and 2 in the endoneurium. The affected vessel wall diameters ranged from 30 to 240 μm. Of 39 vessels with necrosis, the wall thickness was completely involved in 17, and partially in 22 (Fig. 1). In 2 nerves there was evidence of necrosis and healing in different vessels within the same nerve.

Sural nerves. The dominant finding in transverse sections of sural nerve was severe, acute axonal degeneration. The pattern of fibre loss varied, however, according to the degree of ischaemia and the stage at which the nerve was biopsied. In some nerves with less severe ischaemic damage, many surviving myelinated fibres were unaffected but more frequently the nerve fibre loss was severe. In nerves biopsied early in the course of disease acute axonal degeneration involving large numbers of fibres was seen (Fig. 2A). In other nerves biopsied later in the course of the illness the process of axonal degeneration was more complete and few, if any, fibres remained (Fig. 2B). Fibres teased from these nerves were often only fibrous bands and relatively few myelin ovoids remained. In a few nerves the morphological findings of small regenerating fibres seen in transverse sections and on fibre teasing indicated that nerve ischaemia had occurred

TABLE 1 SUMMARY OF CLINICAL AND PATHOLOGICAL FEATURES OF PATIENTS WITH VASCULITIC NEUROPATHY

					Duration of symptoms				
No.	*Biopsy no*	*Age/ sex*	*Duration of follow-up (mths)*	*Cause of death: related (R) unrelated (UR)*	*Systemic (wks)*	*Neuropathic (wks)*	*Type of treatment*	*Type of neuropathy*	*Pathological classification*
Polyarteritis nodosa or hypersensitivity vasculitis									
1	77-72	F70	60	UR	104	2	1	MM	P
2	81-74	M60	6	R	8	8	2	MM	D
3	81-85	F59	24	UR	72	72	3	AN	D
4	75-79	M65	60	UR	8	8	1	MM	D
5	82-42	F79	24	UR	12	12	1	SN	D
6	85-09	M72	36	–	22	20	4	SN	D
7	85-17	F70	2	R	6	6	4	SN	D
8	86-141	F70	8	–	5	5	1	MM	D
9	85-102	F62	6	R	24	8	3	MM	D
10	86-65	F53	10	–	24	2	4	SN	P
11	84-10	M33	60	–	104	52	1	AN	D
Churg-Strauss variant									
12	81-11	F60	19	UR	12	4	1	MM	D
13	78-84	M64	96	–	4	2	4	MM	P
14	80-54	F65	72	–	2	2	1	AN	D
Rheumatoid vasculitis									
15	79-66	M54	96	UR	6	6	3	MM	D
16	78-10	F58	60	UR	24	24	1	MM	D
17	80-75	M71	24	UR	24	24	1	SN	D
18	80-12	M60	60	UR	6	6	2	SN	D
19	82-71	F63	48	–	12	12	2	MM	D
20	80-25	M51	1	R	16	2	5	MM	D
21	86-149	F55	16	–	52	52	4	AN	D
Undifferentiated connective tissue disease									
22	80-16	M49	96	–	4	4	3	MM	D
23	80-01	F76	2	R	6	6	3	MM	D
24	81-60	F78	1	R	4	4	1	MM	A
25	81-10	M76	48	UR	24	6	3	MM	D
26	80-04	M76	78	UR	16	16	1	SN	D
27	82-48	F43	36	–	48	48	1	MM	D
28	82-86	M60	48	–	8	8	1	AN	D
29	85-100	F65	21	–	28	28	1	AN	D
Primary Sjogrens syndrome									
30	81-57	F34	48	–	12	12	2	AN	D
Wegener's granulomatosis									
31	86-76	M63	9	–	48	48	4	AN	D
Chronic lymphocytic leukaemia with cryoglobulinaemia									
32	86-34	F58	13	–	32	32	6	AN	D
Isolated peripheral nervous system involvement									
33	86-78	M47	9	–	–	77	1	SN	D
34	86-04	F66	18	–	–	10	4	AN	D

MM = mononeuritis multiplex, SN = symmetrical sensorimotor neuropathy, AN = asymmetrical neuropathy, D = definite, P = probable; A = absent. 1 = prednisone; 2 = prednisone and azathioprine; 3 = prednisone and chlorambucil, 4 = prednisone and cyclophosphamide; 5 = prednisone, azathioprine and plasmapheresis, 6 = prednisone, cyclophosphamide and plasmapheresis.

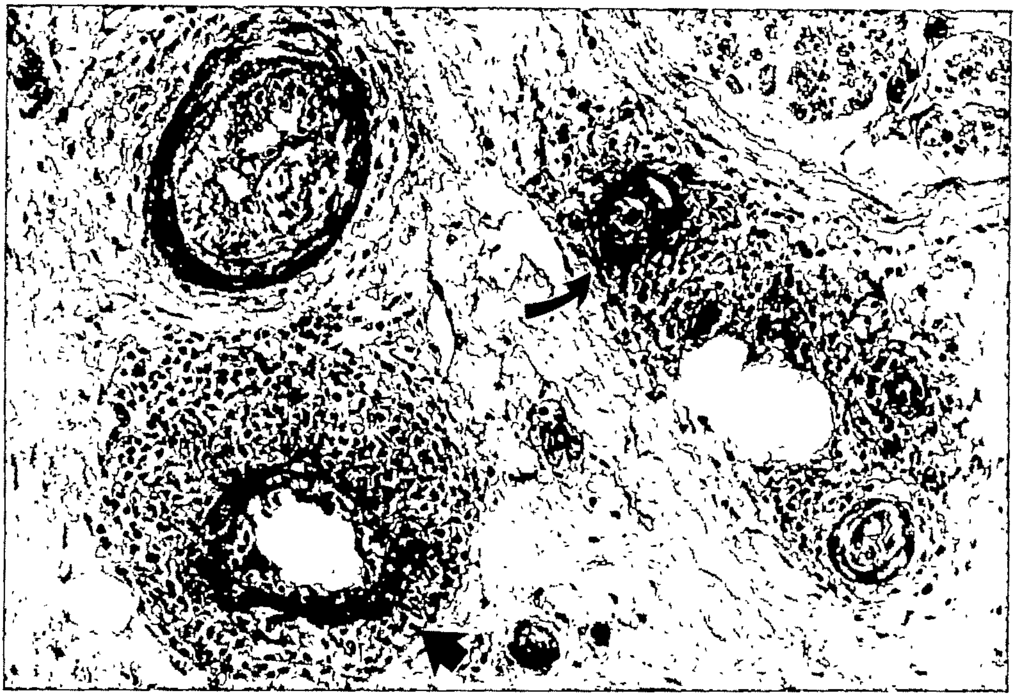

FIG. 1 Transverse section of sural nerve from a patient with polyarteritis. The wall of 1 epineurial arteriole is necrotic and infiltrated with inflammatory cells (large arrow) Above this vessel an arteriole with intimal thickening is seen. A group of smaller arterioles on the right show perivascular cuffing with inflammatory cells and fibrinoid necrosis is seen in 1 vessel (curved arrow); ×33.

at some previous time. In occasional nerves some fascicles were more severely affected than others and in some fascicles remaining nerve fibres were more prominent in peripheral regions.

Morphometric studies were performed on 21 sural nerves (Table 2). The density of myelinated fibres ranged from 16 to 4503 (mean 1493, SD 1468) fibres/mm^2 which may be compared with the control range in our laboratory of 4800–8700 (mean 6640, SD 1300) fibres/mm^2. Analysis of the fibre diameter distributions of remaining fibres demonstrated that fibres of all diameters were affected by the disease process.

Immunofluorescence. Immunofluorescent staining was performed on nerves of 20 patients, all of which reacted positively. In 16 cases immunoglobulin, C_3 and fibrinogen were present on endoneurial or perineurial blood vessels (Fig. 3). In 4 cases only C_3 and fibrinogen were found. In control nerves occasional faint fluorescence was detected with C_3 on endoneurial capilliaries, but there was no fluorescent staining on larger epineurial or perineurial vessels.

Clinical features

Thirty-four patients were studied. The clinical features are summarized in Table 1. The male:female ratio was 1:1.2. The mean age at presentation was 61 yrs (range

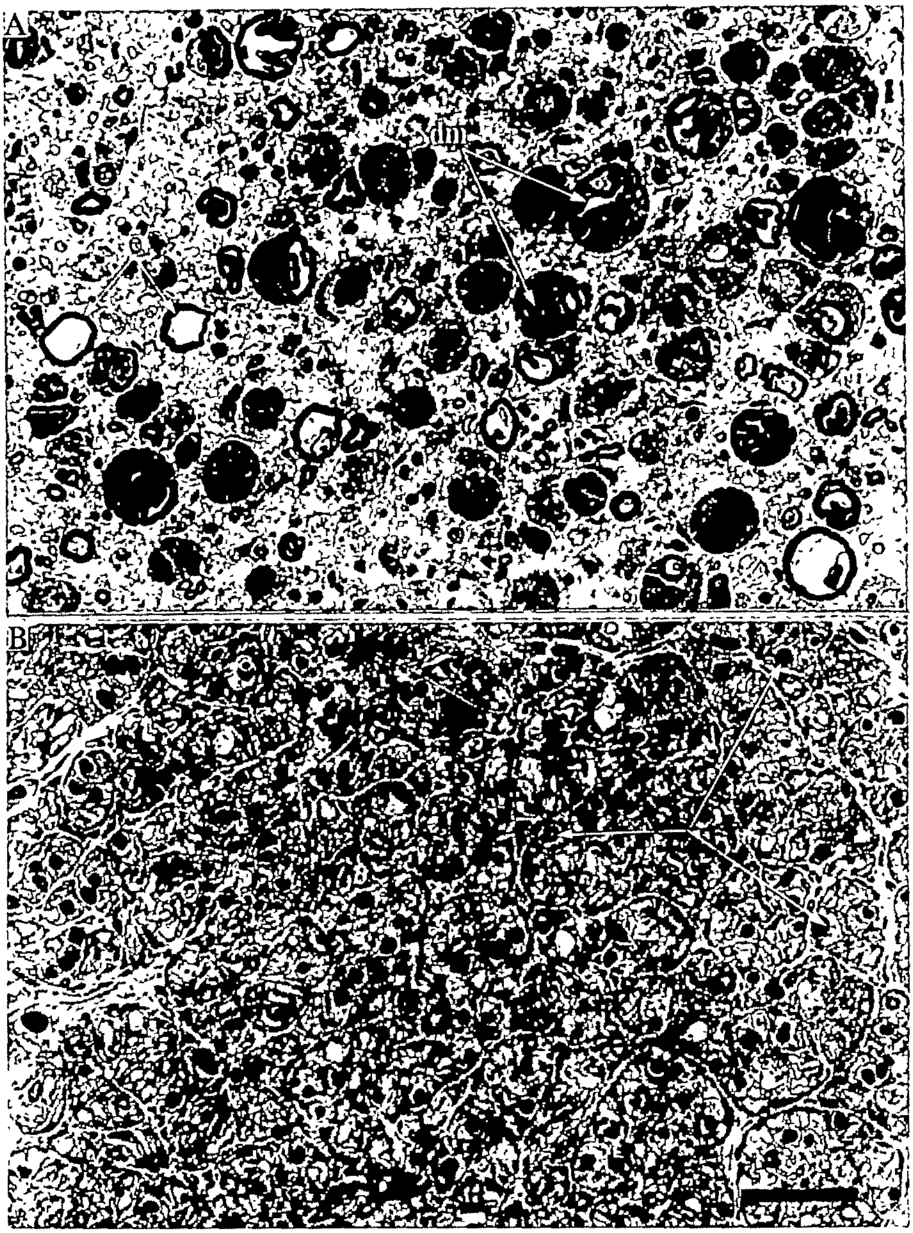

FIG. 2. A, transverse section of sural nerve from a patient with arteritis, showing acute severe axonal degeneration. Numerous degenerating myelin sheaths (dm) are present, in some intact myelin sheaths, there are no axons remaining (e). B, transverse section of sural nerve from a patient with arteritis, showing chronic severe axonal degeneration. There is no myelin remaining, but Schwann cells and Schwann cell nuclei (Sc) persist. Bar = 20 μm

23–79 yrs; SD 11.4 yrs). Symptoms of neuropathy commenced at a mean time of 19 wks (range 2–77 wks; SD 20.7 wks) prior to the diagnosis being made. In patients with systemic disease, symptoms other than those of neuropathy commenced at a mean of

TABLE 2 RESULTS OF MORPHOMETRIC STUDIES ON SURAL NERVE BIOPSIES OF PATIENTS WITH VASCULITIC NEUROPATHY

Case no	*Biopsy no.*	*Density of myelinated fibres (mm^2)*	*Severity of axonal degeneration*	*Cluster formations*	*Proportion of fibres undergoing axonal degeneration*
Polyarteritis nodosa or hypersensitivity vasculitis					
1	77-72	325	Severe	–	–
2	81-74	4326	Moderate	–	90%
3	81-185	16	Severe	–	80%
4	75-59	1677	Severe	–	90%
5	82-42	1315	Severe	+	90%
6	85-09	–	Severe	–	100%
7	85-17	–	Severe	–	100%
8	86-141	–	Severe	–	100%
9	85-102	–	Severe	–	100%
10	86-65	–	Severe	–	100%
11	84-10	3446	Moderate	–	50%
Churg-Strauss variant					
12	81-11	386	Severe	–	25%
13	78-84	634	Severe	–	90%
14	80-54	1027	Severe	+/–	90%
Rheumatoid vasculitis					
15	79-66	230	Severe	–	90%
16	78-10	2700	Moderate	+	20%
17	80-75	4018	Moderate	+	80%
18	80-12	279	Severe	+	50%
19	82-71	667	Severe	0	50%
20	80-25	–	Severe	0	N D
21	86-149	–	Moderate	+	40%
Undifferentiated connective tissue disease					
22	80-16	4503	Moderate	–	30%
23	80-01	922	Severe	–	90%
24	81-60	1869	Moderate	+	80%
25	81-10	625	Severe	+/–	60%
26	80-04	77	Severe	–	90%
27	82-48	308	Severe	–	30%
28	82-86	1996	Severe	+	30%
29	85-100	–	Severe	–	100%
Primary Sjögrens syndrome					
30	81-57	–	Severe	–	90%
Wegener's granulomatosis					
31	86-76	–	Severe	–	100%
Chronic lymphocytic leukaemia with cryoglobulinaemia					
32	86-34	–	Severe	++	10%
Isolated peripheral nervous system involvement					
33	86-78	–	Severe	0	80%
34	86-04	–	Severe	0	85%

Density of myelinated fibres in control nerves, 4800–8700 fibres/mm^2.

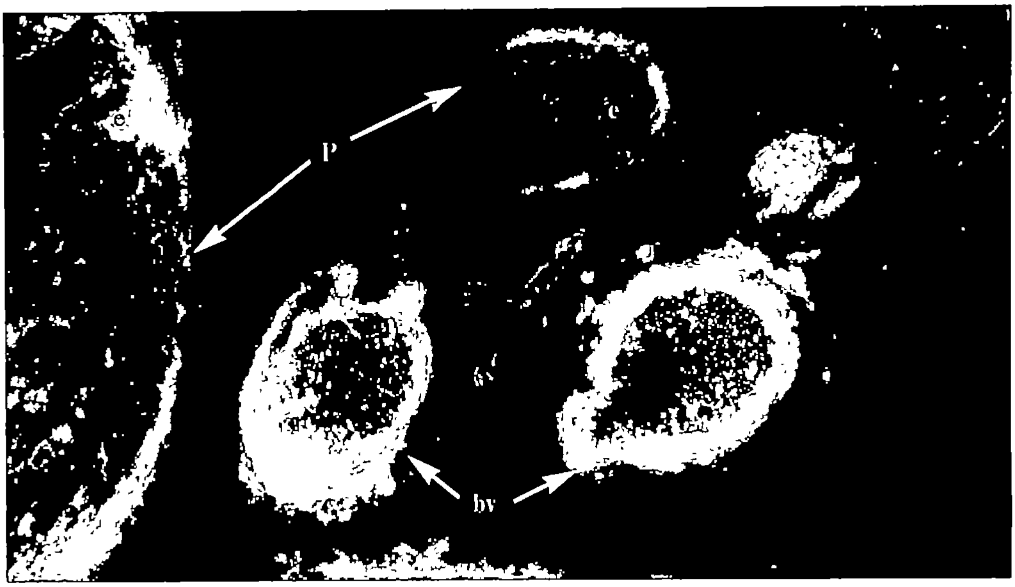

FIG. 3. Two sural nerve epineurial vessels (bv) immunostained for fibrinogen show strong fluorescence There is faint staining of perineurium (P) e = endoneurium, ×750.

24 wks (range 2 – 104 wks; SD 26.6 wks) prior to the diagnosis of vasculitis being made. Pain accompanied other symptoms of peripheral neuropathy in 18 patients (53%). All patients had a sensorimotor peripheral neuropathy. Classical mononeuritis multiplex was seen in 16 patients. Ten patients had an asymmetrical neuropathy and 8 patients had a distal symmetrical peripheral neuropathy. Patients with mononeuritis multiplex had symptoms of neuropathy for a shorter period before the diagnosis was made (mean 9.2 wks; range 2–48 wks; SD 11.7 wks) than patients with either an asymmetrical neuropathy (mean 31.6 wks; range 2–72 wks; SD 23.6 wks) or distal symmetrical neuropathy (mean 20.4 wks; range 2–77 wks; SD 24.1 wks).

Classification of arteritis

Polyarteritis or hypersensitivity vasculitis. Eleven patients had polyarteritis nodosa or hypersensitivity vasculitis based on clinical and pathological data. There were fever and significant weight loss in all patients and abdominal pain was present in 8 patients. Three patients had cutaneous vasculitis. Glomerulonephritis was present in 4 patients, 2 of whom had typical beading of renal arteries at angiography. Muscle biopsies were performed in 3 patients and showed arteritis. Only 3 of 9 patients tested were hepatitis B surface antigen (HBsAg) positive. In 6 of the patients symptoms of peripheral neuropathy were the initial manifestations of systemic vasculitis. In the remaining patients systemic symptoms antedated the neuropathy by a mean of 40 wks (range 2 – 102 wks; SD 32.2 wks).

Churg-Strauss syndrome. Three patients had features of the Churg-Strauss syndrome with asthma, peripheral blood eosinophilia, pulmonary infiltrates, and necrotizing vasculitis. Asthma preceded the onset of neuropathic symptoms by 3 mths to 3 yrs.

Symptoms of neuropathy developed 1 or 2 wks after the onset of systemic symptoms excluding those symptoms associated with asthma.

Rheumatoid vasculitis. Seven patients had rheumatoid vasculitis. Typical rheumatoid arthritis was present for many years prior to the onset of vasculitis (mean 19 yrs; range 5–30 yrs; SD 9.3 yrs). All patients had positive rheumatoid factor, usually in high titre. In all but 1 patient symptoms of neuropathy heralded the onset of systemic vasculitis. Significant weight loss, fevers, abdominal pain, and cutaneous vasculitis were other major features in this group. No patient had evidence of renal or central nervous system disorder.

Undifferentiated connective tissue disease. Eight patients had an undifferentiated connective tissue disease as defined by the presence of systemic symptoms, necrotizing vasculitis, significant titres of antinuclear antibody (ANA) and/or rheumatoid factor (RF) (serum cryoglobulins not detected where tested) and the absence of other clinical or laboratory features characterizing a well-recognized syndrome. In essence, the main difference between this group and patients classified as PAN or hypersensitivity vasculitis was the presence of high titres of ANA or RF or both. Fever and weight loss were present in all but 1 patient. Arthritis was present in 2 patients. Cutaneous vasculitis was seen in 2 patients and cerebral vasculitis in a further 2 patients. Keratoconjunctivitis sicca and glomerulonephritis were present in 1 patient each. Symptoms of peripheral neuropathy were the initial manifestation of systemic illness in all but 1 patient.

Miscellaneous group. Other causes of vasculitic neuropathy identified included Wegener's granulomatosis, primary Sjögren's syndrome and chronic lymphocytic leukaemia with cryoglobulinaemia.

Isolated peripheral nervous system involvement. Two patients had peripheral neuropathy without clinical or laboratory indicators of systemic involvement.

Laboratory investigations

The results of laboratory investigations were not specific. Erythrocyte sedimentation rates ranged from 10 to > 100 mm/h (mean 60 mm/h), only 6 patients having values less than 30 mm/h. Nine patients had mild anaemia. Serological tests have been discussed in the respective disease categories above. Seven patients had lumbar cerebrospinal fluid (CSF) examined. One patient had an absolute elevation in the CSF protein (1.81 g/l) and another with normal protein had oligoclonal IgG on agarose gel electrophoresis. The CSF was normal in the remaining 5 patients. In no case was there a CSF pleocytosis.

Nerve conduction studies

Nerve conduction studies were abnormal in all 34 patients. Mild to moderate slowing of motor conduction and/or reduced amplitude of muscle action potentials were most commonly seen. No muscle action potential was elicited in 25 out of 86 nerves examined in the lower limbs and in 5 out of 47 nerves examined in the upper limbs. Conduction block was detected in nerves of 3 patients (cases 1, 17 and 22), 2 of whom had mononeuritis multiplex. Motor conduction velocities were normal or only mildly slowed, with the exception of 1 patient (case 26) in whom the ulnar motor conduction velocity was 21 m/s. Sensory conduction was abnormal in 27 of 34 patients and absent sensory nerve action potentials in 1 or more nerves was the most common abnormality (no action potential recorded in 46 of 78 nerves tested). The sural nerve action potential was absent in 16 of 20 patients tested; 3 patients had normal sensory action potentials in sural nerves in which there were either probable (2 patients) or definite (1 patient) pathological features of vasculitis. There was electromyographic evidence of denervation in distal muscles of most patients.

Treatment

All 34 patients received treatment with prednisone, either alone (15 patients) or in combination with other immunosuppressive agents or plasmapheresis (*see* Table 1). Prednisone was used in doses of 60–80 mg/d. Cyclophosphamide was given orally in all but 1 patient who was treated with pulse intravenous methylprednisolone and cyclophosphamide according to the protocol of Scott and Bacon (1984). Patients were generally treated for more than 2 yrs. Patients with rheumatoid arthritis usually continued anti-rheumatic drugs. There were few reports of significant side-effects from therapy. One patient died 8 yrs after treatment with chlorambucil, his neuropathy having been quiescent for 6 yrs. Prior to 1985 only 1 patient was treated with cyclophosphamide, chlorambucil then being the alkylating agent of choice.

Follow-up

The patients were followed up from 1 to 96 mths (mean 35.7 mths; SD 29.6 mths) after diagnosis. Seventeen patients (50%) had died. The causes of death and whether the vasculitis appeared active or inactive at the time of death are summarized in Table 3. Six deaths were definitely related to active vasculitis and were most often due to multisystem failure; there was post-mortem confirmation in 3 patients. All these deaths occurred within 6 mths from the onset of illness (mean 3 mths; SD 2.4 mths). Apart from 1 patient who received 50 mg of oral cyclophosphamide for 12 d prior to her death, no other patient treated with this drug died (mean follow-up period 25 mths; range

TABLE 3 CAUSES OF DEATH IN PATIENTS WITH VASCULITIC NEUROPATHY

Case no.	*Age/sex*	*Disease*	*Cause of death*	*Time (mths)*	*Active/inactive*
1	F70	PAN	Cerebral infarction	60	Inactive
2	M60	PAN	Multisystem failure	6	Active
3	F59	PAN	AMI	24	Inactive
5	M65	PAN	Mesothelioma	60	Inactive
6	F79	PAN	AMI	24	Inactive
8	F70	PAN	Multisystem disease	2	Active*
10	F62	PAN	Multisystem disease	6	Active
13	F60	CS	Asthma	19	Inactive
17	M54	RA	AML (chlorambucil)	96	Inactive
18	F58	RA	Unknown	60	Inactive
19	M71	RA	AMI	24	Inactive
20	M60	RA	AMI	60	Inactive
22	M51	RA	Multisystem disease	1	Active*
25	F76	Un	Multisystem disease	2	Active
26	F78	Un	Multisystem disease	1	Active*
27	M76	Un	AMI	48	Inactive
28	M76	Un	Cerebral infarction	78	Inactive

* Post-mortem evidence; PAN = polyarteritis nodosa or hypersensitivity vasculitis, CS = Churg-Strauss variant; RA = rheumatoid arthritis; Un = undifferentiated connective tissue disease; AMI = acute myocardial infarction; AML = acute myeloid leukaemia.

2–96 mths; SD 30 mths). The vasculitis appeared inactive in 11 patients who died on average 50 mths (range 19–96 mths; SD 25.1 mths) after treatment had commenced. It was apparent that all had responded well to treatment and had little neurological disability for long periods prior to their deaths.

From the statistical analyses the only significant prognostic factor identified was age ($P = 0.023$). The type of neuropathy (mononeuritis multiplex, asymmetrical or symmetrical), type of therapy, the patients' sex and the duration of both vasculitic and neuropathic symptoms, were not significant predictors of survival in this series. No attempt was made to analyse the apparent extent of the systemic disease as an independent prognostic determinant.

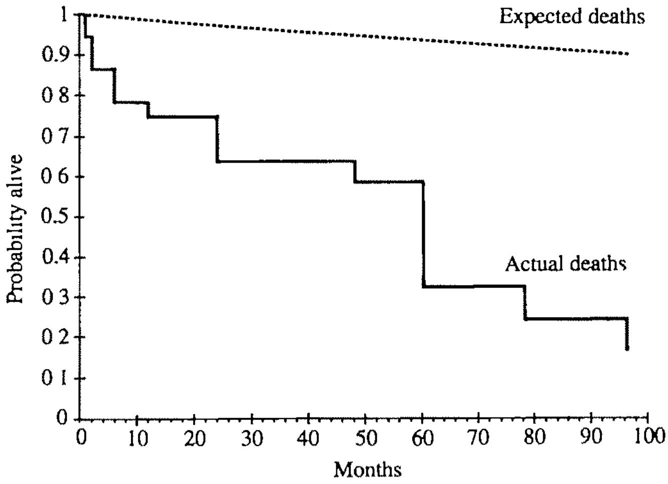

FIG 4. Probability of survival of patients with vasculitis, compared with expected survival data

The survival and expected survival data shown in Fig. 4 demonstrate the poor outcome observed in patients with vasculitic neuropathy. This trend does not appear to diminish with time. The 5-yr survival was 0.37 (SE 0.11), whereas the expected survival was 0.91. To examine whether this was mostly due to early deaths, the analysis was repeated starting at 1 yr with the 23 patients who survived for 1 yr after the illness was diagnosed. The 4-yr survival was 0.47 (SE 0.13), and the expected survival was 0.93. Thus while those who survived the first year appeared to do better, they still fared worse than the general population.

Seventeen patients alive at the time of follow-up were assessed to determine their degree of neurological disability (mean follow-up period 36 mths). All patients had responded to treatment at the time of follow-up, but only 4 patients had ceased therapy altogether, most still being treated with a small dose of prednisone or cyclophosphamide 50 mg/day. No relapses had occurred. Patients were assessed neurologically and their disability graded (Prineas, 1970) (Fig. 5).

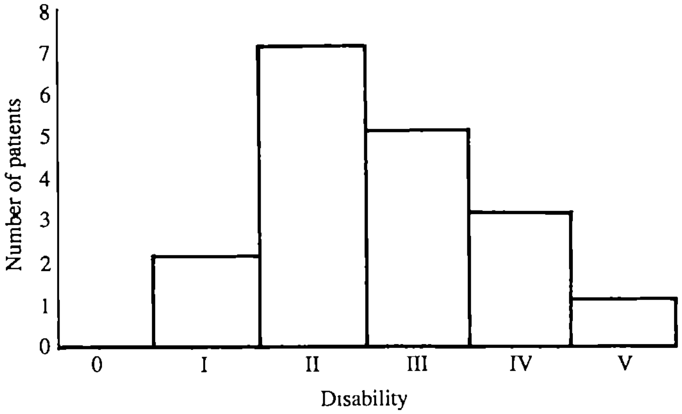

FIG 5 Disability status of patients at final follow-up examination. 0 = no neurological symptoms or signs, I = symptoms but no signs or vice versa; II = mild motor or sensory symptoms and signs, III = moderately disabled by motor and sensory symptoms, including ataxia; IV = requiring assistance with eating or dressing, or using a walking aid, V = not ambulant (Prineas, 1970)

DISCUSSION

Clinical features

The most common causes of vasculitic neuropathy in the present study were polyarteritis nodosa, including the Churg-Strauss variant (32%) undifferentiated connective tissue diseases (24%) and rheumatoid arthritis (20%). Seven cases of vasculitic neuropathy due to systemic lupus erythematosus, previously reported, were not included (McCombe *et al.*, 1987). The findings reflect the high frequency of peripheral nerve involvement in these diseases (Moore and Fauci, 1981; Moore and Cupps, 1983; Conn and Dyck, 1984). A condition of necrotizing vasculitis affecting peripheral nerves without widespread systemic or serological abnormalities has been described (Kissel *et al.*, 1985; Dyck *et al.*, 1987; Said *et al.*, 1988). We encountered only 2 patients with this non-systemic neuropathy.

Mononeuritis multiplex, asymmetrical neuropathy, distal symmetrical sensorimotor neuropathy and plexopathy have been described in patients with vasculitis (Moore and Fauci, 1981; Conn and Dyck, 1984; Kissel *et al.*, 1985; Vincent *et al.*, 1985; Bouche *et al.*, 1986; Harati and Niakan, 1986; Dyck *et al.*, 1987; Said *et al.*, 1988). Our series confirms that mononeuritis multiplex is the commonest clinical manifestation of vasculitic neuropathy (Moore and Fauci, 1981), although asymmetrical neuropathy and distal symmetrical neuropathy occur in a proportion of cases. In most of our patients symptoms of peripheral neuropathy, frequently painful, were the initial manifestations of systemic vasculitis. The diagnosis was made earlier in patients with mononeuritis multiplex. The electrophysiological findings of chronic partial denervation and impaired motor and sensory conduction are similar to those reported by others (Wees *et al.*, 1981; Bouche *et al.*, 1986). Conduction block has been previously reported in vasculitic neuropathy and is attributed to ischaemia (Dyck *et al.*, 1987; Ropert and Metral, 1990). The marked slowing of conduction in 1 nerve may have been caused by multifocal abnormalities.

Pathology

Autopsy studies have demonstrated that the vasculitic process in the peripheral nervous system predominantly affects epineurial arterioles of diameter 50–300 μm leading to a central fascicular pattern of nerve fibre damage, maximal fibre degeneration occurring in the mid thigh and upper arm, regions of relatively poor blood supply (Dyck *et al.*, 1972). These findings are confirmed in our study in which 52 out of 57 affected blood vessels were located in the epineurium, ranging in size from 30 to 240 μm. We found no histological features in the affected blood vessels by which the different clinical disease categories could be distinguished. It was of interest that in all cases deposition of immunoglobulin, C_3 and fibrinogen, or C_3 or fibrinogen only, was seen in blood vessels by immunofluorescence. Kissel *et al.* (1989) found immunofluorescent evidence for immune complex involvement in 85% of the biopsies reported in their series, and only in those vessels which also had intense cellular infiltrates. In our series there were 4 cases without cellular invasion of the sural nerve in which there was immunofluorescent evidence of immune complex deposition. Appropriate immunofluorescent examination of nerve is clearly an important part of the sural nerve histopathological examination when vasculitis is suspected.

The characteristic findings, noted in the present study, of active axonal degeneration in teased nerve fibres, and the presence of asymmetrical involvement between or within fascicles, have been emphasized by Said *et al.* (1988). The frequency of the presence of vasculitic changes in sural nerve biopsies of patients with suspected vasculitic neuropathy is uncertain. Dyck *et al.* (1987) reported that sural nerve biopsy was diagnostic in 58% of patients, but Parry *et al.* (1981) suggest that it is less sensitive. Wees *et al.* (1981) recommend that biopsies should only be performed if the sural nerve sensory action potential is abnormal; however, 1 patient in our series had a normal sural sensory nerve action potential when there was definite vasculitis in the nerve biopsy and a similar case has been reported by Davidson and Sundstrom (1988). We perform biopsy of the sural nerve in patients with peripheral neuropathy when vasculitis is suspected, but do not advocate it as a diagnostic test for arteritis when there is no clinical evidence of peripheral nerve involvement. Vincent *et al.* (1985), who studied nerve and muscle biopsies in 50 patients with vasculitis, found vascular lesions only in the muscle in 26 cases.

Prognosis

We have found that the peripheral neuropathy associated with systemic vasculitis has a good prognosis in terms of functional neurological recovery, a finding similar to that of others (Moore and Fauci, 1981; Chang *et al.*, 1984; Dyck *et al.*, 1987). However, long-term survival (50% dead at a mean follow-up time of 3 yrs) is poor and the presence of neuropathy has little effect on the final outcome.

Prior to the use of corticosteroids in the 1950s, patients with systemic vasculitis had a 5-yr survival of 13% (Report to the Medical Research Council, 1960). Steroids have improved the outlook of patients with this condition, increasing the 5-yr survival to 48–57% (Frohnert and Sheps, 1967; Sack *et al.*, 1975; Chang *et al.*, 1984). The 5-yr survival of 37% in our series is a little worse than these earlier figures and suggests that the more intensive immunosuppression has not improved survival significantly, although in Dyck *et al.*'s (1987) series of 41 patients with systemic vasculitic neuropathy, the survival at 6 yrs was 71%. Several studies of polyarteritis nodosa (Frohnert and Sheps, 1966; Sack *et al.*, 1975; Cohen *et al.*, 1980) did not find that peripheral neuropathy was associated with a worse outcome, except in the case of rheumatoid vasculitis (Cohen *et al.*, 1980).

Our study has demonstrated that there is no reduction in the death-rate over time, a finding that contrasts with previous follow-up studies of systemic vasculitis (Frohnert and Sheps, 1967; Cohen *et al.*, 1980) and a study of mononeuritis multiplex due to vasculitis (Chang *et al.*, 1984). In this latter study it was suggested that if the initial period of active vasculitis is survived, the prognosis will be good. Our data suggest that this is not the case; patients who survived 12 mths had death-rates significantly in excess of those expected from population data.

The larger than expected number of late deaths due to vascular disease in treated patients with systemic vasculitis was observed by Cohen *et al.* (1980). Possible explanations for the occurrence of these deaths are that (1) the vasculitis is active and uncontrolled at the time of death; (2) an unrecognized effect of treatment exists; (3) a complication of vasculitis such as hypertension or renal disease is not adequately treated over a prolonged period; or (4) significant irreversible vascular or parenchymal damage or both occur early in the phase of active vasculitis. The last explanation seems most plausible and it is conceivable that vascular disease might progress over the years, despite the vasculitis being inactive, and lead to late deaths. Existing atheromatous disease may contribute in some way. In our series 80% of late deaths were due to vascular disease. Cohen *et al.* (1980) reported similar findings. Although the existence of recurrent vasculitis is undisputed it is uncommon and there is no convincing evidence that the majority of deaths occurring a year or more after the onset of treatment are due to active vasculitis.

As might be expected we have found that older age positively predicts a worse outcome. This seems very likely to reflect the degree of pre-existing vascular disease and its modification by the vasculitic process. It was difficult to assess other possible predictors of a poor outcome due to the relatively small numbers.

Given the poor prognosis of our patients with systemic vasculitis, we recommend that aggressive treatment should be given as soon as it is apparent that the disease is systemic; it should be assumed that there is generalized blood-vessel involvement and all efforts should be made to control the vasculitic process before extensive irreversible changes occur. In our study the neuropathy of all patients surviving the early phase of the illness improved with treatment, an observation that suggest that the vasculitic process had in fact been suppressed. Improvement in the peripheral neuropathy is therefore to be expected and may be attributed to the regenerative capacity of peripheral nerve axons.

Treatment

Fauci *et al.* (1979) reported an excellent response to oral cyclophosphamide in an uncontrolled study of severe necrotizing vasculitis. Complete remissions were seen in 14 of 17 patients but long-term survival was not assessed. Cohen *et al.* (1980) failed to achieve such good results with oral cyclophosphamide in a small number of patients. Scott and Bacon (1984) in an open trial, found intravenous cyclophosphamide and pulse methyl prednisolone to be more effective than other forms of treatment of systemic rheumatoid vasculitis. Our series also suggests that cyclophosphamide is an effective agent, but clearly large controlled studies are needed.

One controlled study of patients with rheumatoid vasculitis (Nicholls *et al.*, 1973) has shown that azathioprine is no better than placebo. Certainly it appears to be less effective than alkylating agents. There is little information about chlorambucil but it carries a heightened risk of late haematological malignancies.

Conclusion

It is clear that patients with systemic vasculitic neuropathy have a prognosis that is comparable with the overall poor outcome of patients with systemic vasculitis. The neuropathy can be expected to improve and in the long term cause only mild or moderate functional disability. In patients who survive the early phase of the illness, a poor long-term outlook is to be expected and vascular disease will be the chief cause of death.

REFERENCES

AUSTRALIAN LIFE TABLES 1980–1982 (1985) Office of the Australian Government Actuary. Canberra: Canberra Publishing.

BOUCHE P, LÉGER JM, TRAVERS MA, CATHALA HP, CASTAIGNE P (1986) Peripheral neuropathy in systemic vasculitis: clinical and electrophysiologic study of 22 patients. *Neurology, Cleveland,* **36,** 1598–1602.

CHANG RW, BELL CL, HALLETT M (1984) Clinical characteristics and prognosis of vasculitic mononeuropathy multiplex. *Archives of Neurology, Chicago,* **41,** 618–621.

COHEN RD, CONN DL, ILSTRUP DM (1980) Clinical features, prognosis, and response to treatment in polyarteritis. *Mayo Clinic Proceedings,* **55,** 146–155.

CONN DL, DYCK PJ (1984) Angiopathic neuropathy in connective tissue diseases In: *Peripheral Neuropathy.* Second edition. Edited by P. J. Dyck, P. K. Thomas, E. H. Lambert and R. Bunge. Philadelphia and London: W. B. Saunders, pp 2027–2043.

COX DR, OAKES DO (1984) *Analysis of Survival Data.* London: Chapman and Hall.

DAVIDSON JR, SUNDSTROM WR (1988) Sural nerve biopsy in systemic necrotizing vasculitis. *Arthritis and Rheumatism,* **31,** 149–150.

DYCK PJ, CONN DL, OKAZAKI H (1972) Necrotizing angiopathic neuropathy: three-dimensional morphology of fiber degeneration related to sites of occluded vessels *Mayo Clinic Proceedings,* **47,** 461–475.

DYCK PJ, JEDRZEJOWSKA H, KARNES J, KAWAMURA Y, LOW PA, O'BRIEN PC *et al.* (1979) Reconstruction of motor, sensory, and autonomic neurons based on morphometric study of sampled levels. *Muscle and Nerve,* **2,** 399–405.

DYCK PJ, BENSTEAD TJ, CONN DL, STEVENS JC, WINDEBANK AJ, LOW PA (1987) Nonsystemic vasculitic neuropathy. *Brain,* **110,** 843–853.

FAUCI AS, HAYNES BF, KATZ P (1978) The spectrum of vasculitis: clinical, pathologic, immunologic, and therapeutic considerations. *Annals of Internal Medicine,* **89,** 660–676.

FAUCI AS, KATZ P, HAYNES BF, WOLFF SM (1979) Cyclophosphamide therapy of severe systemic necrotizing vasculitis. *New England Journal of Medicine,* **301,** 235–238.

FROHNERT PP, SHEPS SG (1967) Long-term follow-up study of periarteritis nodosa. *American Journal of Medicine,* **43,** 8–14.

GUILLEVIN L, LE THI HUONG DU, GODEAU P, JAIS P, WECHSLER B (1988) Clinical findings of prognosis of polyarteritis nodosa and Churg-Strauss angiitis: a study in 165 patients. *British Journal of Rheumatology,* **27,** 258–264.

HARATI Y, NIAKAN E (1986) The clinical spectrum of inflammatory-angiopathic neuropathy. *Journal of Neurology, Neurosurgery, and Psychiatry,* **49,** 1313–1316.

KISSEL JT, SLIVKA AP, WARMOLTS JR, MENDELL JR (1985) The clinical spectrum of necrotizing angiopathy of the peripheral nervous system. *Annals of Neurology,* **18,** 251–257.

KISSEL JT, RIETHMAN JL, OMERZA J, RAMMOHAN KW, MENDELL JR (1989) Peripheral nerve vasculitis: immune characterization of the vascular lesions. *Annals of Neurology,* **25,** 291–297.

LOW PA, MCLEOD JG, PRINEAS JW (1978) Hypertrophic Charcot-Marie-Tooth disease: light and electron microscope studies of the sural nerve. *Journal of the Neurological Sciences*, **35**, 93–115.

MCCOMBE PA, MCLEOD JG, POLLARD JD, GUO Y-P, INGALL TJ (1987) Peripheral sensorimotor and autonomic neuropathy associated with systemic lupus erythematosus. clinical, pathological and immunological features. *Brain*, **110**, 533–549.

MOORE PM, FAUCI AS (1981) Neurologic manifestations of systemic vasculitis: a retrospective and prospective study of the clinicopathologic features and responses to therapy in 25 patients. *American Journal of Medicine*, **71**, 517–524.

MOORE PM CUPPS TR (1983) Neurological complications of vasculitis. *Annals of Neurology*, **14**, 155–167.

NICHOLLS A, SNAITH ML, MAINI RN, SCOTT JT (1973) Controlled trial of azathioprine in rheumatoid vasculitis. *Annals of the Rheumatic Diseases*, **32**, 589–591.

PARRY GJ, BROWN MJ, ASBURY AK (1981) Diagnostic value of nerve biopsy in mononeuritis multiplex. *Neurology, New York*, **31**, Supplement, 129–130.

PRINEAS J (1970) Polyneuropathies of undetermined cause. *Acta Neurologica Scandinavica*, **46**, Supplement 44, 1–72.

REPORT TO THE MEDICAL RESEARCH COUNCIL BY THE COLLAGEN DISEASES AND HYPERSENSITIVITY PANEL (1960) Treatment of polyarteritis nodosa with cortisone: results after three years. *British Medical Journal*, **i**, 1399–1400.

RODNAN GP, SCHUMACHER HR, ZRAIFLER NJ (1983) Criteria for the diagnosis and classification of the rheumatic diseases. In: *Primer on the Rheumatic Diseases*. Eighth edition. Edited by G. P. Rodnan, H. R. Schumacher and N. J. Zraifler. Atlanta: Arthritis Foundation, pp. 207–212.

ROPERT A, METRAL S (1990) Conduction block in neuropathies with necrotizing vasculitis· *Muscle and Nerve*, **13**, 102–105.

SACK M, CASSIDY JT, BOLE GG (1975) Prognostic factors in polyarteritis. *Journal of Rheumatology*, **2**, 411–420.

SAID G, LECROIX-CIAUDO C, FUJIMURA H, BLAS C, FAUX N (1988) The peripheral neuropathy of necrotizing arteritis: a clinicopathological study. *Annals of Neurology*, **23**, 461–465.

SCOTT DGI, BACON PA, TRIBE CR (1981) Systemic rheumatoid vasculitis: a clinical and laboratory study of 50 cases. *Medicine, Baltimore*, **60**, 288–297.

SCOTT DGI, BACON PA (1984) Intravenous cyclophosphamide plus methylprednisolone in treatment of systemic rheumatoid vasculitis. *American Journal of Medicine*, **76**, 377–384.

VINCENT D, DUBAS F, HAUW J-J, ESCOUROLLE R, GODEAU P, BUGE A *et al.* (1985) Microvasculites nerveuses et musculaires: 50 cas. *Revue Neurologique*, **141**, 440–446.

WALSH JC, MCLEOD JG (1970) Alcoholic neuropathy: an electrophysiological and histological study. *Journal of the Neurological Sciences*, **10**, 457–469.

WEES SJ, SUNWOO IN, OH SJ (1981) Sural nerve biopsy in systemic necrotizing vasculitis. *American Journal of Medicine*, **71**, 525–532.

ZEEK PM (1952) Periarteritis nodosa: a critical review. *American Journal of Clinical Pathology*, **22**, 777–790.

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OBSESSIONAL SLOWNESS

FUNCTIONAL STUDIES WITH POSITRON EMISSION TOMOGRAPHY

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SUMMARY

Patients with Obsessional Slowness (OS) exhibit extreme slowness in the execution of some everyday tasks, such as washing and eating. This may be due to time-consuming rituals, checking behaviour and compulsions. On examination some have neurological signs such as a glabellar tap reflex, cogwheel rigidity or abnormal postures. The purpose of this study was to establish a functional explanation for slowness in this patient group.

We have studied 6 OS patients using positron emission tomography (PET) with ^{15}Oxygen to measure regional cerebral oxygen metabolism and [^{18}F]-6-Fluorodopa (^{18}F-dopa) to assess the integrity of the presynaptic nigrostriatal system. The findings were of focal hypermetabolism in orbital frontal, premotor and midfrontal cortex, whilst dopa uptake into caudate, putamen and medial frontal cortex was normal. The relationship of these findings to the patients' slowness is discussed.

INTRODUCTION

Many patients with Obsessive-Compulsive Disorder (OCD) show a limited degree of slowness in the execution of everyday tasks which is secondary to rituals, other compulsive actions or obsessional thoughts. In some patients, however, slowness dominates the clinical picture and the term 'primary obsessional slowness' has been used (Rachman, 1974). Such patients are meticulous and subject to continual mental checking. Others fractionate complex motor activities (such as cleaning their teeth) into component parts which are then carried out serially with a loss of fluency.

Clinical examination of patients with OS reveals a number of neurological signs, such as a glabellar tap, cogwheel rigidity, upper-limb asynkinesia, simple and complex adventitious movements and perseveration. These motor findings have been described fully in a group of 18 OS patients reported by Hymas *et al.* (1991) (following paper). Whilst some of these signs are classically associated with disease of the extrapyramidal motor system, others may be seen in patients with frontal lobe disease. The purpose of this study was to quantitate regional oxygen metabolism within frontal cortex and dopaminergic function within the nigrostriatal system, to identify functional correlates of these neurological signs, and of the patients' slowness.

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CASE REPORTS

Four of the patients with OS described by Hymas *et al.* (1991) (following paper) and two similar cases are the subject of this study. In all patients a formal diagnosis of obsessive-compulsive disorder was made according to DSM-III R criteria (American Psychiatric Association, 1987). Tables 1 and 2 summarize some of the clinical features of the patients scanned. Further details are given in Hymas *et al.* (1991) (following paper).

Case 1 [*Case O in Hymas et al. (1991), following paper*]

A male aged 37 yrs with a 26-yr history of slowness in most daily activities, taking several hours to turn on the television or open a door. He displayed repetitive ritualistic behaviour and frequent checking and complained of being unable to start things because of 'a kind of inertia'. He had been confined to home for 4 yrs and to bedroom/toilet for 12 mths Drugs at the time of scan: diazepam 20 mg, prothiaden 100 mg and codeine phosphate+paracetamol 6.5 g daily. There was no evidence of neuroleptic treatment.

Case 2 [*Case L in Hymas et al. (1991), following paper*]

A male aged 20 yrs with a 4-yr history of slowness with repetition and slowness in the initiation of movement such as walking through a door He was receiving no drug treatment.

Case 3 [*Case M in Hymas et al. (1991), following paper*]

A male aged 56 yrs with a 25-yr history of slowness, housebound for 10 yrs with repetition of actions and fears of contamination or electrocution Bathing could take up to 12 h On no drug treatment.

Case 4

A male aged 24 yrs with a 8-yr history of slowness, with fears of contamination and checking. Using the toilet to urinate took up to 2 h, opening a door by the handle would take 10 min and switching a light or a tap off 15 min. He worried that his hands had become contaminated with urine and would sometimes spend 12 h at night washing them. He was also mildly depressed. He had received 2 doses of depot

TABLE 1. SUMMARY OF OBSESSIONAL SLOWNESS PATIENTS STUDIED WITH PET

Case no	*Age*	*Duration (yrs)*	*Depressed*	*Drug treatment at time of PET scanning*	*Oxygen metabolism*	*Dopa uptake*
1	37	26	No	Diazepam+Dothiepin	Yes	Yes
2	20	4	No	Nil	Yes	Yes
3	56	25	No	Nil	Yes	Yes
4	24	8	Yes	Lofepramine*	Yes	Yes
5	39	17	No	Nil**	Yes	Yes
6	30	15	No	Pimozide+Clomipramine	Yes	No

*Previously treated with fluphenazine. **Previously treated with chlorpromazine

TABLE 2 SUMMARY OF MOTOR ABNORMALITIES IN OBSESSIONAL SLOWNESS PATIENTS

Case no.	*Age*	*Speech*	*Posture*	*Upper limbs*	*Gait*
1	37	–	+	+	–
2	20	+	+	+	+
3	56	+	+	–	+
4	24	+	+	+	+
5	39	+	+	+	+
6	30	+	+	+	+

For complete details of the motor findings on examination, *see* Hymas *et al.* (1991) (following paper) fluphenazine, 12 and 9 mths prior to his PET scans. This treatment induced bradykinesia, tremor and rigidity which resolved on discontinuation of treatment and prior to PET scanning. Drug treatment at time of scanning: lofepramine 210 mg daily

Case 5

A male aged 39 yrs with a 17-yr history of slowness with difficulty initiating movements such as writing. Getting undressed and into bed took 2 h, brushing his teeth took 20 min and it would take 3 min to open a door by the handle; such everyday activities were disrupted by continual checking. He was stopped by the police on several occasions and asked why he was driving so slowly. He had been treated with chlorpromazine 300 mg daily approximately 18 mths prior to his PET scan but had received no medication for at least a year at the time of scanning.

Case 6 [Case F in Hymas et al. (1991), following paper]

A male aged 30 yrs with a 15-yr history of slowness, being distracted by his surroundings and particularly compelled to touch and pick things up from his path. Bathing took approximately 2 h. At the time of PET scanning, he was taking pimozide 10 mg and clomipramine 10 mg daily

PRACTICAL PROCEDURE

All patients underwent scanning with ^{15}Oxygen labelled CO_2, O_2 and CO to measure regional oxygen metabolism, cerebral blood flow, oxygen extraction ratio and blood volume. Five patients also underwent ^{18}F-dopa scans to measure presynaptic nigrostriatal function. PET scans were performed on the CTI 931/12/8 (CTI, Knoxville, Tennessee, USA) scanner at the MRC Cyclotron Unit at the Hammersmith Hospital The performance characteristics of this scanner have been described by Spinks *et al.* (1988) Ethical permission for these studies and for studies on normal volunteers was obtained from the ethical committee of the Royal Postgraduate Medical School, Hammersmith Hospital. Approval to administer radiolabelled gases and ligands was obtained from the Administration of Radioactive Substances Advisory Committee of the United Kingdom (ARSAC). Written consent was obtained from all subjects after a full explanation of the procedure.

For each study a 22-gauge arterial cannula was inserted into the radial artery after subcutaneous infiltration with bupivicaine 1%. The subject's head was supported and immobilized in an individually moulded polyurethane support and positioned in the scanner with the orbitomeatal line parallel to the detector rings. Subjects were scanned with eyes and ears open, looking towards the dimly illuminated ceiling in a quiet room. A 10 min transmission scan was collected using a retractable ^{68}Gallium/^{68}Germanium ring source.

For oxygen studies, data were collected for two scans each of 10 min duration, during inhalation of $C^{15}O_2$ and $^{15}O_2$ containing 0 75 megabequerels (MBq) ml^{-1}. Ten min washout time followed each scan. A further 6 min scan was collected following a 4 min inhalation of $C^{15}O$. Subjects were instructed to breathe normally during gas inhalation. Parametric images of regional cerebral blood flow, regional cerebral oxygen metabolism, oxygen extraction ratio and regional cerebral blood volume were calculated from the emission scans using arterial oxygen content and whole blood and plasma counts measured in triplicate during each scan (Frackowiak *et al* , 1980; Lammertsma and Jones, 1983).

For ^{18}F-dopa studies, subjects received 100 mg of carbidopa 1 h before the study and a further 50 mg immediately before scanning. Each subject received approximately 140 MBq of ^{18}F-dopa by intravenous infusion over 2 min. Dynamic emission scans were collected for the following 124 min divided into 28 time frames. Both the $^{15}O_2$ and the ^{18}F-dopa scans were reconstructed into 15 planes with a resolution of 8.5×8.5×7.0 mm without interplane deadspace.

Scans were analysed using image analysis software (Analyze version 2.0, BRU, Mayo Foundation, USA) on SUN 3/60 Workstations. For ^{15}Oxygen studies, a series of approximately 600 cortical and subcortical regions of interest was defined and named from the coplanar stereotaxic brain atlas of Talairach and Tournoux (1988). These regions were chosen empirically in order to sample the major anatomical subdivisions of the frontal, temporal, parietal and occipital cortex, cerebellum, striatum and thalamus. For the larger anatomical areas, such as visual association cortex, multiple regions were used. For smaller structures, such as the head of the caudate nucleus, a single region was placed on each of a series of contiguous atlas planes. For each scan the 15 plane image set was interpolated to 43 planes and the degree and angle of displacement from the intercommissural (ACPC) line was measured (Friston *et al.*, 1989). A series of coordinates was then calculated using Microsoft Excel 2.2 (Microsoft Corp., USA) on an Apple Macintosh SE/30 computer (Apple Computer Inc., USA), transferring the 600 atlas coordinates into image space. These regions were transferred to the SUN 3/60 and made available within the Analyze program. Because of the difference in orientation between the images and atlas brains, some of the atlas coordinates fell (when reorientated) midway between adjacent image planes. These coordinates were discarded (approximately 200 in each case), and only coordinates which fell close to the original 15 plane data were accepted as stereotactically positioned. Each of the original 15 image planes was viewed in turn and the position of each region was verified and adjusted in turn to compensate for minor non-linear variations in anatomy, such as those resulting from variations in ventricular size. Each region was of size 4×4 pixels (8.2×8.2 mm) or 5×3 pixels (10.2×6.2 mm) (1 pixel = 2.05 mm). A total of approximately 400 regions were therefore stereotactically placed for each subject, sampling regional activity within the prefrontal region in the greatest detail. Data were generated for each named region and returned to the Macintosh SE/30 for further analysis. The data were averaged according to the anatomical regions listed in Table 3. These regional values were normalized for intersubject variation in global metabolic rate.

For ^{18}F-dopa studies the position of striatal structures was determined by inspection, with reference to the stereotactic atlas of Talairach and Tournoux (1988). Regions of interest were defined for caudate (1 region each side of 4×4 pixels), putamen (3 regions each side of 4×4 pixels, placed contiguously along the axis of the putamen), medial frontal cortex (1 circular region of diameter 8 pixels), occipital lobe (1 circular region each side of diameter 16 pixels) and cerebellum (dimensions as for occipital regions). All regions of interest were defined on two adjacent planes and average values for each anatomical structure were calculated. Regional time activity curves were plotted and the data were analysed using a multiple time graphical analysis approach (Patlak and Blasberg, 1985; Martin *et al.*, 1989). Cerebellar activity was subtracted from striatal activity and the arterial plasma activity curve corrected for the accumulation of 3-O-Methyl dopa, assuming a linear increase in the ratio of 3-O-Methyl dopa:Fluorodopa with time (W. R. Martin, personal communication). An influx constant (K_i) was calculated from the linear regression

TABLE 3 REGIONAL/GLOBAL CEREBRAL METABOLIC RATE FOR OXYGEN

	Normal volunteer (n = 6)		*Obsessional slowness (n = 6)*	
Cortical region (Brodmann no.)	*Left Mean ± SD*	*Right Mean ± SD*	*Left Mean ± SD*	*Right Mean ± SD*
Visual (17)	1.18±0.07	1.09±0.18	1.08±0.14	1.09±0.07
Auditory (41 and 42)	1.12±0.19	1.13±0.17	1.07±0.09	1.04±0.17
Sensorimotor (1–4)	0.92±0.08	0.89±0.03	0.96±0.06	0.96±0.06*
Visual association (18–21, 37)	1.01±0.02	0.99±0.02	1.00±0.03	0.98±0.06
Auditory association (22)	1.08±0.06	1.04±0.12	1.03±0.13	1.06±0.10
Superior parietal (5, 7)	1.01±0.07	0.99±0.09	1.00±0.08	0.98±0.07
Inferior parietal (39, 40)	0.98±0.02	0.97±0.05	1.04±0.05	0.96±0.02
Temporal pole (38)	0.85±0.10	0.85±0.07	0.93±0.08	0.89±0.10
Hippocampus (34)	0.90±0.14	0.74±0.15	0.85±0.05	0.80±0.07
Premotor (6, 8, 44)	0.91±0.04	0.87±0.04	0.96±0.03*	0.95±0.06*
Superior frontal (9)	0.93±0.06	0.92±0.07	0.96±0.06	0.94±0.07
Midfrontal (46)	0.90±0.04	0.90±0.04	0.98±0.06*	0.97±0.05*
Inferior frontal (45)	0.92±0.05	0.95±0.07	1.00±0.11	0.93±0.15
Frontal pole (10)	0.91±0.05	0.88±0.03	0.96±0.05	0.97±0.07*
Orbital (11, 47)	0.91±0.04	0.92±0.03	1.01±0.07*	1.03±0.06**
Medial frontal (32)	0.99±0.04	0.94±0.04	0.96±0.11	0.91±0.15
Anterior cingulate (24)	0.96±0.10	0.85±0.10	0.91±0.07	0.80±0.11
Caudate	0.93±0.09	0.95±0.09	0.94±0.28	1.03±0.08
Putamen	1.11±0.14	1.00±0.11	1.17±0.09	1.10±0.06
Thalamus	1.06±0.06	0.94±0.15	1.05±0.12	0.95±0.08
Cerebellum	0.99±0.13	0.99±0.08	1.10±0.04	1.09±0.08
Corona radiata	0.51±0.21	0.48±0.19	0.38±0.03	0.41±0.06

*Indicates regions for which $P < 0.05$ (*t*-test and Mann-Whitney U test) **Indicates regions for which $P < 0.02$ (*t*-test and Mann-Whitney U test) of regional-cerebellar activity/corrected plasma activity vs integrated corrected plasma activity/corrected plasma activity for data collected between 30 and 120 min after tracer injection (Sawle *et al*, 1990).

A series of 6 healthy male volunteers (age 36 ± 11 yrs) underwent identical studies of regional ^{15}Oxygen metabolism and ^{18}F-dopa uptake. These volunteers were all free of neurological signs. Although they did not undergo extensive neuropsychiatric examination, none described any symptoms of OCD and none had any clinical evidence of slowness. All scored 30/30 on the Mini Mental test (Folstein *et al*, 1975).

RESULTS

Regional cerebral metabolic oxygen metabolism data for patients and controls have been normalized to global metabolic rate and are given in Table 3. Cortical regions are presented according to functional areas, such as primary sensory cortex and association cortex. The prefrontal area has been analysed in the greatest detail, in order to dissect any regional metabolic differences between orbital cortex and other prefrontal regions. Left and right cortical values have been analysed separately. Data are presented for all regions studied including, for example, visual association cortex and thalamus, where we did not expect to find any abnormality.

We have tested for difference in the two group means using an unpaired two-tailed *t* test. Because of small patient numbers and the multiplicity of regions studied we have not applied Bonferroni's correction, as this would render our analysis powerless to detect any small but potentially important group differences. We therefore recognize the potential for a type I error. Because our data might not be normally distributed, we also analysed it using the non-parametric Mann-Whitney U test, which gave similar levels of statistical significance. In Table 3, those regions where $P < 0.05$ or < 0.02 are indicated * and **, respectively. If the P values of < 0.05 were all due to type I errors, however, we would not expect similar cortical regions to be affected in the two hemispheres. The three regions which are bilaterally hypermetabolic in the obsessional slowness patients are orbital frontal cortex (Brodmann 11 and 47), premotor cortex (Brodmann 6, 8 and 44) and midfrontal cortex (Brodmann 46). The individual patient data for these three anatomical areas are shown in Fig. 1. Although there are significant group differences for these regions, there was no single anatomical region for which all of the patient values were greater than all of the control values.

K_i values for ^{18}F-dopa uptake into caudate and putamen for patients and control subjects are given in Table 4. There are no significant differences in striatal ^{18}F-dopa uptake between the patients and control subjects. K_i values for medial frontal cortex and occipital cortex were likewise similar in the two groups (data not shown).

DISCUSSION

The search for functional and pathological correlates of obsessive-compulsive behaviour has been to some extent promoted by observed correlations with other conditions, including diabetes insipidus (Barton, 1976), epilepsy (Kettl and Marks, 1986), birth injury (Capstick and Seldrup, 1977), head injury (McKeon *et al.*, 1984) and encephalitis lethargica (Schilder, 1938). Furthermore, patients with Sydenham's chorea have a higher prevalence of obsessional thoughts and compulsive behaviour than patients with rheumatic fever (Swedo *et al.*, 1989*a*), and patients with frontal gliomas may have transient feelings of compulsion (Ward, 1988). Surgical attention in OCD has focused on the frontal lobe,

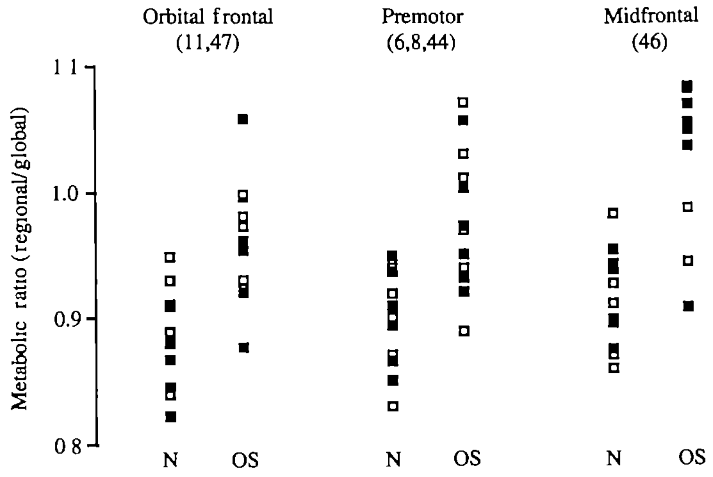

FIG. 1. Scattergraph to show the individual metabolic ratios (region/global) for oxygen metabolism in the three cortical areas found to be significantly hypermetabolic in the obsessional slowness group Left (open squares) and right (filled squares) are shown for each patient N = normal subjects, OS = obsessional slowness patients

TABLE 4 REGIONAL ^{18}F-DOPA K_i*

Region	Obsessional slowness (n = 5) Mean ± SD	Normal volunteer (n = 6) Mean ± SD
Left caudate	0.0164 ± 0.0026	0.0163 ± 0.0027
Right caudate	0.0159 ± 0.0037	0.0159 ± 0.0033
Left putamen	0.0174 ± 0.0039	0.0152 ± 0.0025
Right putamen	0.0165 ± 0.0049	0.0153 ± 0.0030
Medial frontal cortex	0.0034 ± 0.0011	0.0029 ± 0.0011

*K_i values calculated by graphical analysis using plasma as input function.

and indeed partial isolation of either orbital frontal cortex (Bridges *et al.*, 1973) or cingulate cortex (Tippin and Henn, 1982) from surrounding structures has often resulted in clinical improvement.

Previous PET studies

In the context of the above findings, OCD has been studied with PET using ^{18}F-fluorodeoxyglucose to quantify regional glucose metabolic rate (Baxter *et al.*, 1987, 1988; Nordahl *et al.*, 1989; Swedo *et al.*, 1989*b*). The principal findings have been within frontal lobe and caudate. Baxter *et al.* (1987) reported an increase in glucose metabolic rate in OCD within the left orbital gyrus and both caudate nuclei, although the caudate values fell to normal when normalized to the ipsilateral hemisphere. Subsequently, Baxter *et al.* (1988) reported significantly higher glucose metabolic rate in non-depressed OCD patients for whole hemisphere values, right and left orbital cortex and caudate nuclei. The orbital cortex (but not the caudate) values remained elevated after normalization to hemisphere values.

Nordahl *et al.* (1989) studied OCD patients and controls during a continuous auditory discrimination task designed to evaluate the functional localization of sustained attention. A bilateral increase in normalized orbital frontal glucose metabolism was noted in the patient group. No changes were recorded in the basal ganglia. Small and unexplained reductions in glucose metabolism were noted in right parietal and left parieto-occipital regions.

Swedo *et al.* (1989*b*) measured regional glucose metabolism in childhood-onset OCD. Regional metabolic rates were significantly elevated above control values for bilateral prefrontal, left orbital, left premotor, right sensorimotor, left inferior temporal, left paracentral, right cerebellar, right thalamus, left and right anterior cingulate. When normalized to whole hemisphere values, however, only the right prefrontal and left anterior cingulate values remained abnormal. Caudate values were normal in all analyses.

Our findings differ from the above studies in several respects. We report a significant bilateral elevation of orbital cortex (Brodmann 11 and 47), premotor cortex (Brodmann 6, 8 and 44) and midfrontal (Brodmann 46) metabolic rate after normalization to mean ipsilateral cortex values. Hypermetabolism in orbital cortex has been suggested by all four previous studies, and is most likely a finding common to many patients with OCD. In contrast, we believe this is the first report of an abnormality in premotor cortex and midfrontal cortex in this condition. Possible explanations for this include differences in scanner resolution, scanning technique, methods of analysis or a difference in patients studied.

Baxter *et al.* (1987, 1988) have used a camera with lower resolution (11×11×12.5 mm) than this study whilst Swedo *et al.* (1989*b*) have reconstructed their images to a higher transaxial resolution (6×6 mm) yet have a lower axial resolution (10 mm). Reconstructing into a higher resolution reduces the signal-to-noise ratio, and this might have contributed to the Swedo *et al.* (1989*b*) finding of scattered areas of hypermetabolism throughout both hemispheres. The four previous studies all measured glucose metabolism, whereas we measured oxygen metabolism. Glucose and oxygen metabolism are normally closely coupled, and it is unlikely that this difference in technique is significant. Accurate anatomical localization within PET data depends upon both axial and transaxial resolution. Baxter *et al.* (1987, 1988) and Swedo *et al.* (1989*b*) assumed that the brain has a constant alignment to the inferior orbitomeatal line and positioned their regions-of-interest by eye using an atlas of brain sections taken in that plane. In view of our greater axial (and transaxial) resolution, we were able to accurately image the intercommissural line and hence align our image data with a set of transformed atlas coordinates. Inter-subject averaging of data from studies where anatomical regions have been stereotactically positioned may improve signal-to-noise ratio further. Nordahl *et al.* (1989) studied their patients during an auditory discrimination task. This seems not to have affected the findings of orbital frontal hypermetabolism (a finding common to all of these studies). The only finding peculiar to their study was the report of parietal and parieto-occipital hypometabolism, which may be either related to the activation paradigm used, or perhaps to the exploratory statistical approach adopted in most of these studies.

Clearly the statistical power of the observation of hypermetabolism in midfrontal and premotor cortex is low and this finding should be confirmed through replication before we can be certain of its validity. If genuine, however, we suggest that these areas of hypermetabolism might reasonably be included within the neural substrate of our patients' slowness.

The motor effects of frontal cortex lesions

The effect of lesions within premotor cortex in man have been described in patients with cerebral tumours or following cerebral infarction. Freund and Hummelsheim (1985) described a disorder of movement with proximal arm weakness and a limb-kinetic apraxia. They noted that 'the movement disorder became apparent when a certain temporal sequence of activities of proximal muscles of both sides was necessary for a movement'. Passingham (1987) discusses the subdivision of premotor areas in the direction of movement. He suggests that the lateral premotor cortex (lateral Brodmann 6) directs movement on the basis of visual and auditory cues from the outside environment, and that the supplementary motor area (medial Brodmann 6) directs actions on the basis of proprioceptive cues concerning the animals's own actions. Patients with obsessional slowness are unable to move at normal speed when left alone, yet under direction from others may improve their speed to near-normal levels.

Eslinger and Damasio (1985) reported a patient following an extensive frontal resection to remove a meningioma. The patient became indecisive and extremely slow: 'He took about 2 h to get ready for work in the morning and some days were consumed entirely by shaving and hair washing.' CT and MRI studies showed bilateral damage to orbital and medial frontal cortex and subcortical white matter, and damage to the dorsolateral cortex on the right side only. Not surprisingly, a ^{133}Xenon single photon emission tomography (SPET) study showed low flow corresponding to the area of ablation.

Goldman-Rakic (1987) has reviewed evidence regarding motor functions of cortex around the principal sulcus (Brodmann 46 in man, Walker 46 in monkey). This area has prominent connections with basal ganglia and deep layers of the superior colliculus, with reciprocal connections to supplementary motor area (SMA) and the premotor cortex. It is suggested that the principal sulcus can influence delayed-responding, though only when inner models of reality are used to govern responses is the prefrontal cortex pre-eminently engaged. This is of relevance to our obsessional slowness patients, as they are constantly planning movements which may be extremely delayed in execution. With external prompting, however, this delay may often be circumvented with an increase in the speed of movement.

We have studied our patients at rest, and yet they have hypermetabolism within premotor cortex. We also recorded an increase in metabolic rate within primary sensorimotor cortex (Brodmann 1 to 4) on the right side only. In healthy volunteers these areas can be activated during repetitive movement, with an increase in regional cerebral blood flow in both primary motor cortex and SMA (Fox *et al.*, 1983; Roland, 1987). This area is hypermetabolic in patients with obsessional slowness even at rest, and it would be of interest to measure regional changes during self-paced and externally paced movement in these patients.

A slowly increasing negative potential, recorded over the fronto-central scalp 1–2 s prior to self-paced movements in healthy subjects has been termed the readiness potential or bereitschaftspotential (Deecke *et al.*, 1969). It has been suggested that there are at least two principal generators of this potential, the supplementary motor area and the primary motor cortex, the former probably bilateral and the latter contralateral to subsequent movement (Deecke, 1987). The hypermetabolism in premotor cortex (including the supplementary motor area) in obsessional slowness patients may thus be related to an elaboration of the neural substrate of this potential. To our knowledge, such electrophysiological recordings have not been performed in these patients.

Given that these patients report a lengthened preparation for movement and furthermore have increased oxygen metabolism within some frontal regions, we still have no explanation for why normal movement does not proceed. Synaptic firing within midfrontal cortex, orbital cortex and premotor cortex might be inhibitory rather than excitatory, perhaps relating to the blockade of movement rather than its preparation.

Dopa studies

Baxter *et al.* (1987) reported an increase in caudate glucose metabolism in acute OCD patients, whilst Swedo *et al.* (1989*b*) found normal values in young adults with childhood-onset OCD. It was suggested that the caudate might be hypermetabolic in early disease, with metabolic rate falling to normal when the disease becomes entrenched. Luxenberg *et al.* (1988) measured caudate and lenticular volume in OCD, reporting a lower caudate volume in patients than in controls. Weilburg *et al.* (1989) described a patient with obsessive-compulsive disorder in whom magnetic resonance imaging revealed a decrease in volume of the left caudate and a band of prolonged T_1 and T_2 signal in the left putamen, although the patient had a history of birth trauma requiring neonatal intensive care, and these findings may have been incidental to his OCD. Laplane *et al.* (1984, 1989) reported 8 patients with lentiform lesions, mostly within the pallidum. All were thought to be the consequence of anoxic or metabolic encephalopathy. These patients exhibited inertia with loss of drive and in some cases compulsive and obsessional behaviour. Seven of the patients had ^{18}F-fluorodeoxyglucose PET studies which revealed a relative hypometabolism of striatum and prefrontal cortex. Whilst these findings contrast with the *hyper*metabolism in patients with classical OCD, the anatomical congruency is striking.

Two of us (N.F.H. and A.J.L.) have observed a shortlived response to L-dopa in some patients with obsessional slowness. In view of this observation, the rich connections of caudate and putamen with frontal cortex (Yeterian and Van Hoesen, 1978) and the motor consequences of striatal disease, we were anxious to examine both metabolic rate and ^{18}F-dopa uptake in striatal tissue.

Striatal ^{18}F-dopa accumulation represents uptake into nerve terminals, conversion into ^{18}F-dopamine by dopa decarboxylase, and subsequent concentration and storage in terminal neurotransmitter vesicles (Firnau *et al.*, 1987). Although several approaches to the quantitative analysis of ^{18}F-dopa uptake have been developed (Martin *et al.*, 1989; Sawle *et al.*, 1990; Tedroff *et al.*, 1990), none is able to measure endogenous dopamine synthesis as the conversion of tyrosine to L-dopa is the rate limiting step in the dopamine synthetic pathway. Nevertheless, a reduction in ^{18}F-dopa uptake is believed to reflect a reduction in the number of functioning nigrostriatal dopaminergic neurons. Patients with early Parkinson's disease may have a minimal evidence of akinesia and yet at the time of presentation have lost 50–80% of nigrostriatal neurons (Jellinger, 1987). ^{18}F-dopa scans show a major reduction of striatal uptake in such patients (Leenders, 1986). The normal ^{18}F-dopa uptake in primary obsessional slowness patients suggests that their extreme slowness is not related to a loss or dysfunction of nigrostriatal dopaminergic neurons. Although several patients were taking benzodiazepine or antidepressant medication at the time of their ^{18}F-dopa scans, none had received major tranquillizers for a considerable period of time. The effect of medication upon the scan results is not known although we are unaware of any evidence suggesting that this medication would give a spuriously high ^{18}F-dopa uptake, masking a true reduction of nerve terminal function.

Relationship between obsessional slowness and Parkinson's disease

Most of the neurological signs recorded in our patients, such as positive glabellar tap or stooped posture, are common findings in Parkinson's disease. Whilst we have no evidence for a nigrostriatal dopaminergic defect in these patients, the structures in which we have demonstrated oxygen hypermetabolism are involved in both the 'complex' loop (pre-frontal cortex → caudate → globus pallidus and substantia nigra → ventral anterior thalamus → prefrontal cortex) and the 'motor' loop (premotor and sensory-motor cortex → putamen → globus pallidus and substantia nigra → ventrolateral thalamus → premotor and sensorimotor cortex), two of the principal neuronal circuits involving the basal ganglia (DeLong *et al.*, 1983). The mechanism of the short-lived clinical improvement seen in some patients after treatment with L-dopa is unclear but presumably is related to function within these circuits.

In summary, our obsessional slowness patients have bilaterally increased oxygen metabolism at rest in orbital frontal cortex, premotor cortex and midfrontal cortex. Orbital frontal hypermetabolism has been reported in four previous studies of OCD, whereas hypermetabolism within premotor and midfrontal cortex is a novel finding. We suggest that this increased activity is related to these patients' internal preparation for movement.

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REFERENCES

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders*. Third edition, revised. DSM-III-R. Washington, DC: American Psychiatric Association

Barton R (1976) Diabetes insipidus and obsessional neurosis. *American Journal of Psychiatry*, **133**, 235–236.

Baxter LR, Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE (1987) Local cerebral glucose metabolic rates in obsessive-compulsive disorder: a comparison with rates in unipolar depression and in normal controls. *Archives of General Psychiatry*, **44**, 211–218.

Baxter LR, Schwartz JM, Mazziotta JC, Phelps ME, Pahl JJ, Guze BH *et al.* (1988) Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *American Journal of Psychiatry*, **145**, 1560–1563.

Bridges PK, Goktepe EO, Maratos J (1973) A comparative review of patients with obsessional neurosis and with depression treated by psychosurgery. *British Journal of Psychiatry*, **123**, 663–674.

CAPSTICK N, SELDRUP J (1977) Obsessional states: a study in the relationship between abnormalities occurring at the time of birth and the subsequent development of obsessional symptoms. *Acta Psychiatrica Scandinavica*, **56**, 427–431.

DEECKE L (1987) Bereitschaftspotential as an indicator of movement preparation in supplementary motor area and motor cortex In: *Motor Areas of the Cerebral Cortex. Ciba Foundation Symposium* 132 Edited by G. Bock, M. O'Connor and J. Marsh. Chichester: John Wiley, pp 231–250.

DEECKE L, SCHEID P, KORNHUBER HH (1969) Distribution of readiness potential, pre-motion positivity, and motor potential in the human cerebral cortex preceding voluntary finger movements. *Experimental Brain Research*, **7**, 158–168.

DELONG MR, GEORGOPOULOS AP, CRUTCHER MD (1983) Cortico-basal ganglia relations and coding of motor performance. *Experimental Brain Research*, **49**, Supplement 7, 30–40.

ESLINGER PJ, DAMASIO AR (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology, Cleveland*, **35**, 1731–1741.

FIRNAU G, SOOD S, CHIRAKAL R, NAHMIAS C, GARNETT ES (1987) Cerebral metabolism of 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine in the primate. *Journal of Neurochemistry*, **48**, 1077–1082.

FOLSTEIN MF, FOLSTEIN SE, MCHUGH PR (1975) 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

FOX PT, FOX JM, RAICHLE ME, BURDE RM (1985) The role of cerebral cortex in the generation of voluntary saccades: a positron emission tomographic study. *Journal of Neurophysiology*, **54**, 348–369.

FRACKOWIAK RSJ, LENZI GL, JONES T, HEATHER JD (1980) Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure, and normal values. *Journal of Computer Assisted Tomography*, **4**, 727–736.

FREUND H-J, HUMMELSHEIM H (1985) Lesions of premotor cortex in man. *Brain*, **108**, 697–733.

FRISTON KJ, PASSINGHAM RE, NUTT JG, HEATHER JD, SAWLE GV, FRACKOWIAK RSJ (1989) Localisation in PET images: direct fitting of the intercommissural (AC-PC) line. *Journal of Cerebral Blood Flow and Metabolism*, **9**, 690–695

GOLDMAN-RAKIC PS (1987) Motor control function of the prefrontal cortex. In. *Motor Areas of the Cerebral Cortex. Ciba Foundation Symposium* 132. Edited by G. Bock, M. O'Connor and J. Marsh. Chichester: John Wiley, pp. 187–200.

HYMAS N, LEES A, BOLTON D, EPPS K, HEAD D (1991) The neurology of obsessional slowness. *Brain*, **114**, 2203–2233.

JELLINGER K (1987) The pathology of parkinsonism. In: *Movement Disorders* 2. Edited by C. D. Marsden and S. Fahn. London: Butterworths, pp. 124–165.

KETTL PA, MARKS IM (1986) Neurological factors in obsessive compulsive disorder: two case reports and a review of the literature. *British Journal of Psychiatry*, **149**, 315–319.

LAMMERTSMA AA, JONES T (1983) Correction for the presence of intravascular oxygen-15 in the steady-state technique for measuring regional oxygen extraction ratio in the brain: 1. Description of the method. *Journal of Cerebral Blood Flow and Metabolism*, **3**, 416–424.

LAPLANE D, BAULAC M, WIDLOCHER D, DUBOIS B (1984) Pure psychic akinesia with bilateral lesions of basal ganglia. *Journal of Neurology, Neurosurgery and Psychiatry*, **47**, 377–385

LAPLANE D, LEVASSEUR M, PILLON B, DUBOIS B, BAULAC M, MAZOYER B *et al.* (1989) Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions: a neuropsychological, magnetic resonance imaging and positron tomography study. *Brain*, **112**, 699–725.

LEENDERS KL, PALMER AJ, QUINN N, CLARK JC, FIRNAU G, GARNETT ES *et al.* (1986) Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. *Journal of Neurology, Neurosurgery and Psychiatry*, **49**, 853–860.

LUXENBERG JS, SWEDO SE, FLAMENT MF, FRIEDLAND RP, RAPOPORT J, RAPOPORT SI (1988) Neuroanatomical abnormalities in obsessive-compulsive disorder detected with quantitative X-ray computed tomography. *American Journal of Psychiatry*, **145**, 1089–1093

MCKEON J, MCGUFFIN P, ROBINSON P (1984) Obsessive-compulsive neurosis following head injury: a report of four cases. *British Journal of Psychiatry*, **144**, 190–192.

MARTIN WRW, PALMER MR, PATLAK CS, CALNE DB (1989) Nigrostriatal function in humans studied with positron emission tomography. *Annals of Neurology*, **26**, 535–542.

NORDAHL TE, BENKELFAT C, SEMPLE WE, GROSS M, KING AC, COHEN RM (1989) Cerebral glucose metabolic rates in obsessive compulsive disorder. *Neuropsychopharmacology*, **2**, 23–28

PASSINGHAM RE (1987) Two cortical systems for directing movement. In: *Motor Areas of the Cerebral Cortex. Ciba Foundation Symposium* 132. Edited by G. Bock, M. O'Connor and J. Marsh. Chichester: John Wiley, pp. 151–164.

PATLAK CS, BLASBERG RG (1985) Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data Generalizations. *Journal of Cerebral Blood Flow and Metabolism*, **5**, 584–590.

RACHMAN S (1974) Primary obsessional slowness *Behaviour Research and Therapy*, **12**, 9–18.

ROLAND PE (1987) Metabolic mapping of sensorimotor integration in the human brain. In: *Motor Areas of the Cerebral Cortex. Ciba Foundation Symposium* 132. Edited by G. Bock, M. O'Connor and J. Marsh. Chichester: John Wiley, pp. 251–268.

SAWLE GV, COLEBATCH JG, SHAH A, BROOKS DJ, MARSDEN CD, FRACKOWIAK RSJ (1990) Striatal function in normal aging: implications for Parkinson's disease. *Annals of Neurology*, **28**, 799–804.

SCHILDER P (1938) The organic background of obsessions and compulsions. *American Journal of Psychiatry*, **94**, 1397–1416.

SPINKS TJ, JONES T, GILARDI MC, HEATHER JD (1988) Physical performance of the latest generation of commercial positron scanner. *IEEE Transactions on Nuclear Science*, **35**, 721–725.

SWEDO SE, RAPOPORT JL, CHESLOW DL, LEONARD HL, AYOUB EM, HOSIER DM *et al.* (1989*a*) High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *American Journal of Psychiatry*, **146**, 246–249.

SWEDO SE, SCHAPIRO MB, GRADY CL, CHESLOW DL, LEONARD HL, KUMAR A *et al.* (1989*b*) Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Archives of General Psychiatry*, **46**, 518–523.

TALAIRACH J, TOURNOUX P (1988) *Co-planar Stereotaxic Atlas of the Human Brain.* New York: G. Thieme.

TEDROFF J, AQUILONIUS S-M, LAIHINEN A, RINNE U, HARTVIG P, ANDERSSON J *et al.* (1990) Striatal kinetics of [^{11}C]-(+)-nomifensine and 6-[^{18}F]fluoro-L-dopa in Parkinson's disease measured with positron emission tomography. *Acta Neurologica Scandinavica*, **81**, 24–30.

TIPPIN J, HENN FA (1982) Modified leukotomy in the treatment of intractable obsessional neurosis. *American Journal of Psychiatry*, **139**, 1601–1603

WARD CD (1988) Transient feelings of compulsion caused by hemispheric lesions: three cases. *Journal of Neurology, Neurosurgery and Psychiatry*, **51**, 266–268.

WEILBURG JB, MESULAM M-M, WEINTRAUB S, BUONANNO F, JENIKE M, STAKES JW (1989) Focal striatal abnormalities in a patient with obsessive-compulsive disorder. *Archives of Neurology, Chicago*, **46**, 233–235.

YETERIAN EH, VAN HOESEN GW (1978) Cortico-striate projections in the rhesus monkey: the organization of certain cortico-caudate connections. *Brain Research, Amsterdam*, **139**, 43–63

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THE NEUROLOGY OF OBSESSIONAL SLOWNESS

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SUMMARY

Seventeen of 59 patients admitted to hospital for treatment of Obsessive-Compulsive Disorder (OCD) were found to have significant slowness, mainly due to difficulty in initiating goal-directed action and suppressing intrusive and perseverative behaviour. In this subgroup subtle neurological abnormalities were found more frequently than in healthy controls and included loss of motor fluency, hesitancy of initiation of limb movements, speech and gait abnormalities, cogwheel rigidity, complex repetitive movements and tics. Difficulties in cognitive set-shifting and complex spatial-and-shifting abilities were found on neuropsychological testing, but no correlation was found between these disturbances and either the degree of obsessionality or the severity of motor dysfunction. These results suggest that patients with obsessional slowness may have a dysfunction in the frontal-basal-ganglia loop system.

INTRODUCTION

Obsessions are recurrent, persistent ideas, thoughts, images or impulses that are experienced as involuntary, senseless or repugnant. Attempts are made to ignore or suppress them. Compulsions are repetitive and seemingly purposeful behaviours that are performed according to certain rules or in a stereotyped fashion. The act is performed with a sense of subjective compulsion often coupled with a desire to resist the compulsion. The individual usually recognizes the senselessness of the behaviour and does not derive pleasure from carrying out the activity, although it often provides a release of tension (American Psychiatric Association, 1980).

This is theme from which are woven all those many variations of individual psychopathology to be found under the general rubric of Obsessive-Compulsive Disorder (OCD). Common obsessions concern violent urges towards the self or others, fears of contamination of self or others, or doubts about past actions or events. Common compulsive rituals involve cleaning, counting, checking, touching or avoidance (Dowson, 1977; Stern and Cobb, 1978; American Psychiatric Association, 1980).

In recent decades it has not been customary to try to understand such symptoms and behaviour as manifestations of cerebral dysfunction. Indeed, in systems of psychiatric nosology such as DSM-III (American Psychiatric Association, 1980) or ICD-9 (World Health Organization, 1978), the absence of demonstrable brain disease was a criterion by which the syndrome of OCD was defined. Classified as a 'neurosis', it took its place alongside a variety of other disorders which, according to contemporary usage of the term, were often thought to be best approached primarily with the languages and concepts of dynamic psychology or sociology and with little reference to those of physiology or clinical neurology.

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However, since Esquirol in 1838 described a patient under his care who displayed some of those particular features of behaviour and experience which subsequently came to be termed 'obsessive-compulsive disorder' (Esquirol, 1838), there has existed a current of observation, thought and speculation which has always sought to convey, alongside descriptions of a purely psychological nature, the relevance of neurological mechanisms (Hymas and Prasad, 1989). Pierre Janet, for example, whose descriptions of the syndrome must remain unsurpassed in their comprehensiveness, elegant clarity and attention to psychological nuance, nevertheless perceived the provisional and partial nature of his psychological formulations, and believed them to be paving the way to a future anatomical understanding (Janet, 1903).

Janet's awareness and acknowledgement of the importance of the biological and neurological aspects of the syndrome, and the similar awareness shown by contemporaries such as Tuke (1894) or Jackson (1895), perhaps reflected the shared concepts of neurology and psychiatry, and the easy commerce of ideas which existed between their practitioners, in the latter half of the 19th century (Bynum, 1985; Dowbiggin, 1985). The subsequent impact of Freudian ideas led to, or at least was an expression of, a divergence of viewpoints which increasingly persuaded psychiatrists to divorce mental illnesses such as obsessive-compulsive disorder from the neurological context of earlier understanding. The 'neuroses' assumed an autonomy as 'functional' psychological disorders (Berrios, 1985) and became freed from those connotations of central nervous system disease which had been implicit in earlier conceptions of the term (Hunter, 1973; Bynum, 1985; Rogers, 1987).

The literature on OCD tended, thereafter, to remain predominantly psychological in emphasis. However, in the first half of this century, speculations concerning the cerebral basis of the syndrome continued. Such ideas were especially fuelled by the observation of obsessive-compulsive phenomena in patients suffering from neurological disorders. The outbreaks of epidemic encephalitis which had swept Europe and North America at the end of the First World War and throughout the following decade (Greenfield, 1976) had been of particular importance in yielding many reports of obsessions and compulsions associated with the syndrome of post-encephalitic parkinsonism (e.g. von Economo, 1931). Obsessions and compulsions associated with epilepsy (e.g. Brickner *et al.*, 1940) and tic-disorder (e.g. Creak and Guttman, 1935) were also reported, and within the limits of contemporary knowledge attempts were made to interpret both the neurological and the psychiatric disturbances in terms of shared cerebral mechanisms. Schilder, for example, in his study of 1938 referred to the association of obsessive-compulsive phenomena with epidemic encephalitis earlier in the century and argued for a close relationship between the neurologically-based disturbances of motility seen in these patients and their particular psychiatric symptoms (Schilder, 1938). He estimated from his clinical experience that in obsessional patients, without any history suggestive of encephalitis, 'organic' signs could be found in about a third of cases, and that in a further third the symptomatology aroused the suspicion of an organic background. The signs that Schilder observed included: rigidity of the face, flexor rigidity of the arms, tremor, impaired eye convergence, great urge to talk and propulsive features in speech, and what he called 'motor urges of a higher degree'.

A renewed interest in the importance of these earlier observations to the study of obsessive-compulsive disorder can be discerned in some recent publications (Laplane *et al.*, 1981, 1984; Yaryura-Tobias and Neziroglu, 1983; Cummings and Frankel, 1985; Ward, 1988). Furthermore, some more recent studies have attempted to generate 'biological markers' of the disorder, or of subgroups within it. However, few investigations have proceeded from coherent hypotheses concerning brain-behaviour relationships, and few have attempted to explain the phenomena of OCD in terms of phenomena displayed by patients, or experimental animals, suffering from cerebral disorders whose mechanisms may be better understood (Hymas and Prasad, 1989).

Against this background, the comparatively recently described phenomenon of 'obsessional slowness' gains particular interest. Many patients with obsessive-compulsive disorder complain of slowness in carrying out their ordinary, day-to-day activities, a slowness which may sometimes be profoundly incapacitating (Marks, 1978). It is commonly thought to be the result of the performance of rituals and has attracted little attention in its own right. Indeed, in standard textbook descriptions of the disorder, for example, those by Slater and Roth (1969), Ey *et al.* (1974) or Rado and Monroe (1974), it receives no explicit mention.

In 1974 Rachman described what he termed 'primary obsessional slowness' (Rachman, 1974). His report was based on the characteristics of 10 patients who showed severe slowness in the execution of the simple tasks of daily living, such as dressing, bathing or eating. His descriptions, however, leave some uncertainty about the precise phenomenon he was attempting to identify. On the one hand, he notes that particular care was taken to exclude patients 'in whom slowness was plainly a secondary consequence of extensive checking or other rituals', yet elsewhere states that 'needless to say, all 10 of the patients were carrying out some checking behaviour'. On the one hand, he describes that the patients resembled a 'slow motion movie', yet on the other that 'slow motion of the limbs seemed to play no part in their overall slowness'. Rachman explains the slowness psychologically in terms of 'meticulousness', and without reference to the brain.

Our own interest in obsessional slowness was kindled by the close observation of a patient who demonstrated the phenomenon to a marked degree. This 25-yr-old man, who suffered from a compulsion to touch things and repeat actions, would take hours over the most ordinary of activities such as having a bath or dressing. His slowness seemed to derive from a difficulty in initiating simple movements, in shifting between and sequencing different patterns of movement, and in performing more than one movement simultaneously; his goal-directed behaviour was continually disrupted by the perseveration of unwanted movements and by an extreme distractability to random visual stimuli; a further striking feature was the inefficacy of his verbal monitoring in modifying and directing his behaviour. The patient, therefore, showed a number of deficits of motor performance and control reminiscent of some of those seen in, for example, frontal lobe disorders, or Parkinson's disease in which a dysfunction of basal ganglia and possibly also of frontal lobe mechanisms is believed to be important.

This background was felt to justify a prospective investigation of a series of prominently slow obsessive-compulsive patients using a design which would expose some of those motor and cognitive deficiencies seen in patients suffering from dysfunction of the frontal lobes of the brain and their subcortical connections.

METHODS

Subjects

Patients. Patients were recruited from the Behaviour Therapy Unit of the Bethlem and Maudsley Hospital, London. Between November 1985 and April 1988 all patients referred to the unit for inpatient assessment and/or treatment of obsessive-compulsive symptoms and behaviour were screened at the time of their first attendance or admission. In all cases the diagnosis of OCD was made according to DSM-111 guidelines (American Psychiatric Association, 1980). However, in view of the potential interest of patients who might show a conjunction of this particular psycho-syndrome and a 'neurological' disorder, the exclusion criteria of the presence of Gilles de la Tourette syndrome or 'organic mental disorder' were ignored. This matches the subsequent revision of DSM-111 (DSM-111-R, American Psychiatric Association, 1987) In all cases the obsessive-compulsive symptoms and behaviours constituted the leading feature of the psychiatric picture and formed the principal reasons for the patient's referral. Fifty-nine patients were screened of whom 32 were men, with a mean age of 35.2 yrs (range 17–73, SD 14.49), and 27 were women, with a mean age of 33.5 yrs (range 21–65, SD 11 5).

Two other patients who fulfilled this study's diagnostic criteria for obsessional slowness (*see below*) were also included. The first was the 25-yr-old man mentioned in the Introduction (*see also* Appendix, case A), and the second was a 36-yr-old woman (case L) who was currently under the inpatient care of one of us (A.L.) at the National Hospital for Nervous Diseases In addition to the obsessions, compulsions and slowness which dominated the clinical picture and were the main reasons for her admission, she also carried a diagnosis of Gilles de la Tourette syndrome.

Controls. For the neuromotor examination of those patients displaying 'slowness' (*see below*) a control group was recruited from hospital staff and employees. The controls and patients were matched pairwise with the patients for age, sex and IQ as judged by the National Adult Reading Test (NART) (Nelson, 1982) The pairs were completely matched for sex and the majority were matched within 3 yrs of age and 3 IQ points For the neuropsychological assessments, controls matched by group for age and sex, were selected from a population recruited for an earlier study. No control had a history of psychiatric or physical illness. Informed consent was obtained from all patients and controls for the procedures of the study.

Assessments

Assessments consisted of an initial screening procedure followed by the further study of patients showing slowness.

Initial screening

All patients were asked to complete the Maudsley Obsessional-Compulsive Inventory (MOCI) (Hodgson and Rachman, 1977), and the self-administered written form of the Leyton obsessional inventory (LOI) (Cooper, 1970; Snowdon, 1980). These are two widely used methods of assessing the existence and extent of obsessive-compulsive complaints. In order to simplify the administration of the questionnaires, the questions relating to resistance and interference in the Leyton inventory were omitted. All patients were also asked to complete a slowness questionnaire which had been devised for the study.

Slowness questionnaire. This self-administered questionnaire is shown in Fig. 1. It lists 20 common items of behaviour. The subject is asked to rate the speed of his or her own performance of each item in comparison with an average person. The scoring method is shown on the questionnaire. The maximum possible score is 60, corresponding to the maximum severity of subjective slowness.

A pilot study was conducted to establish the score above which 'slowness' would be defined as present. The questionnaire was administered to 6 obsessive-compulsive patients in whom slowness in day-to-day activities was a prominent and disabling feature. Patients in this group often complained of having to take several hours over such routine tasks as dressing, eating a meal, washing or bathing. Their results were compared with a group of 11 other obsessive-compulsive patients not showing this feature to a marked degree. The mean score of the slow group was 38.3 (SD 7.2, range 30–47), and that of the non-slow group 12.2 (SD 8.8, range 3–29). A score of 30, which lay approximately 2 standard deviations above the mean of the non-slow group, was chosen as the criterion score above which a significant degree of slowness in day-to-day activities was to be defined as present for the purpose of the study.

Instructions The following is a list of activities which people with your kind of problem have difficulty with. Please answer each question by putting a tick under the appropriate number Then for each activity give an estimate of the time it takes you.

0 I have no problem with this activity-it takes me about the same time as the average person

1 This activity takes me about twice as long as most people

2 This activity takes me about three times as long as most people

3 This activity takes me more than three times as long as most people

0	1	2	3	ACTIVITY	TIME TAKEN
				Having a bath or shower	
				Washing hands and face	
				Care of hair (combing, washing, etc)	
				Brushing teeth	
				Dressing	
				Undressing	
				Using the toilet to urinate	
				Using the toilet to defaecate	
				Getting out of bed in the morning	
				Eating a meal	
				Cleaning a room in the house	
				Making a bed	
				Opening a door by the handle	
				Switching a light or a tap on or off	
				Locking or closing a door or window	
				Writing a letter to a friend	
				Putting a letter in the post-box	
				Walking from one room to another	
				Walking 100 yards down the street	
				Crossing the road	

FIG 1. Slowness questionnaire

Further study of patients showing significant slowness

Standard neurological examination. All patients were seen and examined independently by a psychiatrist (N.H.) and a neurologist (A.L.), and a standard neurological examination performed. In addition, the neurologist assessed each patient for asynkinesia using a test similar to that devised by Schwab *et al.* (1954). The subject was required to draw a triangle with the dominant hand whilst simultaneously pressing the bulb of a sphygmomanometer with the other to cause a rise in the column of mercury. Performance was assessed for ease and fluency of simultaneous movement, and rated as either normal or impaired

Motor examination. This structured and detailed examination was performed by the psychiatrist (N.H.), but in 15 cases the complete procedure was audio- and videotaped. These tapes were then independently examined by the neurologist (A.L.), and agreement on the various features which had been rated was estimated in 12 cases (*see below*). The neuromotor control group was then examined by one of us (N.H.). The 10 items of this examination, in order of administration, are listed below. Care was first taken to put each subject at ease by full explanation of the procedure. In each case the subject had met the doctor performing the examination on many previous occasions and a rapport of willingness and cooperation was readily established. Each item was rated for a variety of features using the following numerical scale: 0 = no abnormality, 1 = slight abnormality, 2 = moderate abnormality, and 3 = marked abnormality.

(1) *Speech* A structured interview was administered and responses recorded to obtain a sample of speech. All questions concerned 'neutral' factual demographic detail, for example, the subject's age, place of birth, nationality, parents' occupations, etc., and tasks such as counting from 0 to 50, or saying the days of the week, were also given. The features rated were hesitancy of reply, slowness of speech, low volume of voice and reduced pitch-variation.

(2) *Posture.* During the above interview the subject was filmed in a seated posture both frontally and laterally. Following the interview the subject was asked to stand with arms first by the side and then held outstretched and in front of the body. The features rated were the degree of spontaneous facial movement, the general level of spontaneous bodily movement, and any degree of postural flexion

(3) *Head, neck and face elicited movement* The subject was asked to shake the head from side to side, put the tongue in and out of the mouth, put the tongue out of the mouth and move it quickly from side to side, open and close the eyes and finally to bare the teeth. Frontal close-up recordings of the head and neck were made. Each movement was demonstrated three times by the examiner Hesitancy of initiation, fluency and slowness were the features rated.

(4) *Upper limb rapid alternating movements.* The subject was asked to hold out one hand in the shape of a fist and to make, on the back of the fist, rapid alternating supination-pronation movements with the flat of the other hand, followed by rapid, light tapping movements with the finger-tips of this hand on the back of the fist The procedure was then repeated with the hands reversed. The subject was then asked to perform rapid open-and-close movements of the tips of the forefinger and thumb of one hand, separating these digits as much as possible between each opposition, followed by rapid opposition movements between the tips of the thumb and each finger in turn. Each movement was demonstrated by the examiner three times, and performance in both hands assessed. The features rated were hesitancy of initiation, slowness, fluency, decay of amplitude and decay of speed

(5) *Upper limb sequential movements.* Ozeretski's test was used (Luria, 1976). With the subject in a seated position, both hands are placed in a pronated position in the lap, one in the shape of a fist and the other with fingers extended; using simultaneous movements of the hands, the subject is asked to rapidly alternate their positions. Fist-ring test: using the dominant arm and hand, first the hand shaped into a fist is held out and withdrawn, followed by the hand with forefinger and thumb shaped into a ring; these movements being alternated several times. Fist-edge test: using the dominant hand, the hand is placed on the lap, first pronated in the shape of a fist, and then semi-prone with the fingers extended and the medial edge resting on the lap. These movements are alternated several times. Fist-edge-palm test: this is similar to the movements of the fist-edge test but with the addition to the sequence of a third movement in which the hand is moved from the 'edge' position to full pronation of the extended hand in the lap. The three-movement sequence is repeated several times. All the above movements are demonstrated three times by the examiner. The features rated were hesitancy of initiation, slowness and fluency

(6) *Test-tube task* For this task the subject was seated at a table immediately in front of a row of 24 plastic test-tubes, each measuring 10.5 cm in length and 1.5 cm in diameter, and aligned perpendicularly to the table's leading edge. At a further distance of 15 cm was placed a rigid wire test-tube rack measuring 14 cm in width, 9.5 cm in depth and 9.5 cm in height, and containing 24 slots corresponding to the test-tubes The subject, using the dominant hand, was required to place each test-tube in the rack as quickly and as accurately as possible. A practice placement of three test-tubes was allowed before beginning the task to ensure full understanding of instructions. The features of performance rated consisted of hesitancy of initiation, slowness and fluency.

(7) *Writing.* The subject was seated at a table before a pen and a piece of plain A4 paper and asked to pick up the pen and write the word 'sunshine' as many times as possible for 1 min. The features rated were hesitancy of initiation, slowness, fluency and abnormal writing posture

(8) *Foot tap.* In a seated position, the subject was asked to lightly tap each foot on the floor as quickly as possible. The features rated were hesitancy of initiation, slowness and fluency.

(9) *Whole-body movements.* Starting from a seated position with both feet placed firmly on the floor, the subject was asked to alternately rise to a standing position and sit down again as many times as possible for 15 s. The subject, from a standing position, was then asked to balance first on one leg for 10 s, and then on the other. The features rated for whole-body movements were hesitancy of initiation and slowness.

(10) *Gait.* The subject was asked to walk briskly on the flat along a concreted pavement for a distance of approximately 15 m to the bottom of a series of 6 stone steps, climb the steps, turn round and return to the starting point. The features of gait which were rated were hesitancy of initiation, slowness, pace-length, degree of right arm-swing, degree of left arm-swing and abnormality of turn.

Inter-rater reliability

Video-tapes of 12 patients were assessed independently by the 2 raters (A.L. and N.H.) on each of the 10 items of the above examination. For each item a 4-point global score of severity was derived and reliability estimated using the Weighted Kappa Coefficient as described by Cohen (1968) The maximum weight of 8 was given to the most serious disagreement where 1 rater scored no abnormality (0) and the other scored marked abnormality (3). Where 1 rater scored no abnormality (0) and the other scored slight (1) or moderate (2) the weights assigned were 2 and 4 respectively. If both raters observed an abnormality but differed in their rating by 1 deg of severity the weight assigned was 1. Relatively low coefficients were achieved for foot-tap (0.446) and writing (0.573), though others were in an acceptable range of 0.629–0.938.

Neuropsychology

The following tests were employed, based on the rationale described by Head and colleagues (Head *et al.*, 1989):

National adult reading test (Nelson and O'Connell, 1978; Nelson, 1982; Crawford *et al.*, 1987, 1988; O'Carroll *et al.*, 1987).

Wisconsin card sorting test (Grant and Berg, 1948; Milner, 1963).

Verbal fluency tests (Milner, 1964, Borkowski *et al.*, 1967; Benton, 1968, 1976, Newcombe, 1969)

Stylus maze test (Milner, 1964). The subject is seated before a board on which is mounted an array of 100 nail-heads, and required to trace with a stylus a predetermined route across the board. The stylus is wired to the nails in such a way that contact with any nail-head outside the correct route produces a noise from a buzzer to inform him of his error The subject is not informed of the route and must proceed by trial and error using the buzzer as a guide. He is not allowed to retrace his steps, retrace the correct path, or move diagonally. Testing proceeds until 3 error-less runs are achieved.

Money road map test of directional sense (Butters *et al.*, 1972). The subject is shown a street map on which are traced two routes, one involving 3 right or left turns, the other involving 32 such turns. The subject is asked to imagine walking each route and to indicate at each street intersection whether he would turn right or left. He is not allowed to turn the map or his body in order to facilitate his answers The short route is followed first as a practice task to ensure full understanding of the rules of the test. The number of correct responses is scored.

Personal orientation test (Semmes *et al.*, 1963) The subject is shown a series of 5 cards each of which carries 2 diagrams of the human body, 1 in anterior and 1 in posterior view. On each diagram 4 areas on the right or left side of the body are numbered. The subject is required to point on his own body, in the order of the numbers, to the parts numbered in the diagrams.

Line orientation test (Benton *et al.*, 1978). The subject is shown a series of 15 cards each carrying a fan-shaped array of 11 lines of equal length, numbered 1 to 11 and separated by angles of 18°. Above each of these reference diagrams are 2 stimulus-lines corresponding in orientation to 2 of the lines in the reference diagram below, and of half the length. The subject is required to detect which reference lines the 2 stimulus-lines correspond to, a correct response being scored if both stimulus-lines are correctly identified. The test is free of any sequencing or switching of rules or mental images, and thus reflects a relatively 'pure' spatial ability. It is reported to be sensitive to posterior right hemisphere dysfunction.

Block design. This was taken from Wechsler's adult intelligence scale tests (Wechsler, 1958).

Assessment of depression

Patients were asked to complete the Beck depression inventory (BDI) (Beck *et al.*, 1961, Metcalfe and Goldman, 1965).

RESULTS

Initial screening

All 59 consecutive patients completed the slowness questionnaire (SQ). Seventeen (29%) scored greater than 30, the criterion at or above which slowness was to be defined as present for the purpose of the study.

Two patients in the consecutive non-slow subgroup failed to return the Leyton inventory (LI) and 1 patient in the slow subgroup refused to complete it. One patient in the non-slow subgroup returned an incomplete Maudsley Obsessive-Compulsive Inventory (MOCI) which was excluded from the analysis.

Some characteristics of the patient and control groups are summarized in Table 1. With the measures of obsessionality used in this study the initial group of 59 consecutive patients was comparable with previously reported populations of adults with obsessive-compulsive disorder (Cooper, 1970; Hodgson and Rachman, 1977; Murray *et al.*, 1979).

TABLE 1. CHARACTERISTICS OF PATIENTS AND CONTROLS

	Whole group	*Non-slow group*	*Slow group*	*Adjusted slow group*	*Neuromotor controls*	*Neuropsychological controls*
Males	32	22	10	7	10	8
Females	27	20	7	4	6	7
Age (yrs)	34.5 (13.1)	33.4 (12.43)	36.9 (14.8)	34.7 (16.7)	36.7 (14.0)	32.9 (10.5)
Verbal IQ (NART)			114.6 (8.5)	113.5 (7.87)	116.4 (6.68)	114.2 (7.7)
Slowness questionnaire	19.5 (16.5)	10.5 (8.2)	41.7 (8.4)	43.4 (8.83)		
Leyton—Total	37.5 (12.9)	35.2 (13.4)	43.3 (9.7)	45.1 (8.53)		
Symptoms	26.0 (9.4)	24.1 (9.5)	30.9 (7.2)	32.4 (6.7)		
Traits	11.5 (4.3)	11.2 (4.5)	12.4 (3.7)	12.7 (3.2)		
MOCI—Total	15.6 (5.9)	14.3 (5.9)	18.8 (4.7)	21 (3.9)		

Comparison of slow and non-slow subgroups. The slow subgroup did not differ significantly from the non-slow subgroup either in sex distribution ($\chi^2 = 0.2$, df = 1, $P > 0.05$) or age ($t = 0.93$, df = 57, $P > 0.05$). The slow subgroup differed significantly from the non-slow subgroup in the total LI score (symptoms+traits) (Mann-Whitney U = 210, Z = 2.00, $P < 0.05$, two-tailed), the LI symptom score (Mann-Whitney U = 190, Z = 2.35, $P < 0.02$, two-tailed) and the MOCI total obsessionality score (Mann-Whitney U = 236.5, Z = 2.43, $P < 0.02$, two-tailed), the slow subgroup showing greater obsessionality as judged by these measures. There was no significant difference between the subgroups on the LI trait score (Mann-Whitney U = 328, Z = 0.54, $P > 0.05$).

Further study of the slow subgroup

Two of the 17 consecutive patients in this group refused to participate further. Two other patients (cases A and L) who were comparable in their scores on the slowness questionnaire and obsessional inventories were substituted as described in Methods. Reanalysis of all the slow vs non-slow comparisons showed no effect of the substitution on the results. The group of 17 slow patients subjected to the further studies described below therefore comprises these 2 patients and the remaining 15 consecutive patients. Vignettes of these patients are provided in the Appendix.

Clinical features of the slow group

The leading obsessive-compulsive features were classified into objective behaviour and subjective symptoms. These are summarized in Table 2.

TABLE 2 CLINICAL FEATURES OF PATIENTS WITH SLOWNESS (n = 17)

	Case code																	
	A	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*N*	*O*	*P*	*Q*	
Observable behaviour																		
Simple actions repeated, e.g. switches, taps, doors	+	+			+		+	+				+	+	+		+	+	(59)*
Simple actions preceded or interrupted by hesitation	+	+		+	+	+	+		+				+	+	+	+		(65)
Simple actions 'ritualistic'		+						+								+		(18)
Increased touching of environment	+				+					+								(18)
Decreased touching/avoidance of environment			+	+					+		+		+		+	+	+	(47)
Increased response to random visual stimuli	+								+									(12)
Visual checking or searching behaviour	+	+	+						+				+			+		(35)
Increased response to random auditory stimuli										+				+				(12)
Repetitive cleaning/washing of self			+	+	+				+		+		+	+	+		+	(53)
Repetitive cleaning/washing of personal environment											+						+	(12)
Difficulty going through doorways	+	+			+	+	+	+	+									(41)
Rigid routines and order for simple actions				+	+	+		+				+		+				(35)
Subjective experiences																		
Fear of harming others, e g by contamination										+	+			+	+		+	(29)
Fear of being harmed, e g. by contamination	+	+	+	+			+	+	+		+	+	+		+		+	(71)
Ruminations					+	+	+		+			+				+		(35)
Doubts													+	+				(12)
Feeling of incompletion of action	+	+		+			+					+	+				+	(41)
Counting to self				+										+				(12)
Perfectionism						+							+	+				(18)
Indecision					+	+												(12)

*Numbers in parentheses show the percentage of the group displaying each feature.

In addition to the diagnosis of OCD, which was the principal psychiatric feature in every case and the reason for the patient's referral, another psychiatric diagnosis could be sustained in 1 case where the obsessive-compulsive features arose in a setting of probable Asperger's syndrome. The group mean score on the Beck depression inventory was 17.3 (SD 10.4, range 4–44). Twelve patients scored 18 or below corresponding to the responses of a 'mildly depressed' population in the original study by Beck and colleagues (Beck *et al.*, 1961). Four patients (cases J, N, O and P) scored 22–28 corresponding to 'moderate' depression; 1 patient (case D) scored 44 corresponding to 'severe' depression though a diagnosis of major depression was not sustained on examination.

In addition to the psychiatric diagnosis, a neurological diagnosis could be sustained in 4 cases. Cases F and O had a parkinsonian syndrome. In 1 case this probably began in childhood, there was no tremor, and no disturbance of pace-length or handwriting. In the other the development of classical Parkinson's disease was preceded by many years of a typical OCD with contamination fears and repetitive hand-washing. The patient commented that for years she had moved slowly and carefully in order to avoid touching objects which might contaminate her and regarded it as ironic that now she wished to move more quickly she was unable to do so. Cases J and L had motor and vocal tics.

Case P had received a course of ECT 2 wks prior to examination and was receiving imipramine at the time of assessment. Case L had received tranylcypromine until 2 wks before examination. Case K had received phenelzine until 2 wks before assessment. At the time of examination case D was taking 20 mg of diazepam and 100 mg dothiepin daily, case H was receiving zuclopentixol 16 mg daily, and case N was receiving depot flupenthixol 40 mg monthly. No other case had been taking medication for several weeks before examination.

Four patients, but also 4 controls, gave histories of an abnormal birth. All patients had normal CT brain scans.

Motor examination

Motor abnormalities. Comparisons between patients and controls are given in Table 3. Two analyses were performed: firstly, the slow patient group as a whole was compared with controls; secondly, an 'adjusted slow group' was compared by excluding 6 cases with features in addition to their OCD which could have been independently associated with motor disorder, and could have been biasing the findings in favour of the hypothesis being examined. These were the 4 cases in whom an additional 'neurological' diagnosis could be sustained (Gilles de la Tourette syndrome in cases J and L, and a parkinsonian syndrome in cases F and O), and the 2 cases (H and N) who were taking neuroleptic medication at the time of examination.

In the slow patient group as a whole, motor abnormalities were seen in all of the 10 categories of the examination but were most common on examination of upper-limb rapid alternating movements, of upper-limb sequential movements and of gait. In the controls, abnormalities were observed only on examination of head, neck and facial movements, of upper limb rapid alternating movements, of upper limb sequential movement and of gait. Using Wilcoxon's signed-ranks test (two-tailed), comparison with the control group showed significantly more abnormalities in the patients for all

TABLE 3 NEUROMOTOR EXAMINATION—COMPARISON OF PATIENTS AND CONTROLS

	Group means (±SD)			
Item[1]	*Patients*	*Controls*	*W*[2]	*P*
Speech	2.00±2.3	0	0	< 0.005
	[1.73±1.7	0]	[0	< 0.02]
Posture	1.75±2.1	0	0	< 0.005
	[1.27±1.2	0]	[0	< 0.02]
Head/neck/face	1.50±2.5	0.31±0.8	5	n.s.
	[0.73±1.5	0.36±0.9]	[3	n.s.]
Upper limb rapid alt. movements	3.00±3.1	0.31±0.8	6	< 0.01
	[1.64±2.1	0.36±0.9]	[5	n.s.]
Upper limb seq. movements	3.13±3.1	0.06±0.25	2.5	< 0.001
	[2.36±2.9	0.09±0.30]	[2	< 0.02]
Test-tube task	1.38±1.9	0	0	< 0.01
	[0.55±0.9	0]	[0	No decision possible]
Whole body	1.06±1.7	0	0	< 0.02
	[0.45±0.7	0]	[0	No decision possible]
Gait	3.13±4.2	0.25±0.45	4	< 0.02
	[2.09±2.5	0.36±0.50]	[4	< 0.05]
Total motor scores	19.8±19.2	1.19±1.6	1	< 0.0001
	[12.3±7.4	1.18±1.5]	[1	< 0.001]
Timed motor tests				
Written words per minute	12.6±3.4	19.1±2.6	6.510	< 0.0005
	[14.2±2.4	19.0±2.8]	[4.284	< 0.005]
Stand-sits in 15 s	5.4±1.8	8.0±1.4	3.602	< 0.005
	[6.2±1.5	7.6±1.5]	[1.606	n.s.]
Test-tube task time in s	60.0±23.5	43.3±5.0	1.943	< 0.05
	[50.0±7.1	45.0±6.1]	[1.054	n.s.]

[1] Writing and foot tap omitted because of relatively poor inter-rater reliability. [2] Two-tailed Wilcoxon's signed-ranks test. Values in square brackets show results of analysis after removal of case F, H, J, L, N and O (for explanation, *see* Results section). [3] One-tailed related *t*-test Values in square brackets show results of analysis after removal of cases F, H, J, L, N and O (for explanation, *see* Results section). n.s. = not significant

categories except head/neck/face movements. Although the selection criteria for slowness were subjective, in all 3 objectively-timed motor examinations (number of words written in 1 min, number of stand-sits performed in 15 s, time to perform the test-tube task) the patient group as a whole was significantly slower than the controls.

A reanalysis excluding the 6 cases as described above removed the significant difference between patients and controls in tests of upper-limb rapid alternating movement. Because of small numbers, no statistical decision was possible comparing the two groups in the test-tube task and whole body movement scores. However, objective speeds in the latter

2 tests were no longer significantly different between patients and controls. In comparison with controls, patients remained significantly impaired in their total motor score, and in scores for speech, posture, upper limb sequential movement and gait. They also remained significantly slower than controls in the timed writing test.

Other abnormal neurological findings

After exclusion of the 6 cases as described above, the following abnormalities were found in the remaining 11 'uncontaminated' patients: five patients (cases B, D, E, I and M) had a positive glabellar tap; case B had seborrhoea; 2 cases (K and M) had increased blinking and case I had decreased blinking; case D had a rapid, fine tremor of the left hand when outstretched; case K had mild cogwheel rigidity at the wrists during movement of the contralateral limb. Four patients (cases C, K, M and Q) had upper limb asynkinesia.

Speech abnormalities other than those recorded in the structured motor examination were noted in 2 patients: case I spoke in an unduly 'clipped', deliberate and precise manner; case D showed moderate pressure of speech.

Spontaneous, sudden, brief and simple movements affecting, for example, the face, head, neck or limbs, and intruding into the free flow of changes in posture and behaviour, were noted in 2 patients: case B showed jerking of the head and arms, and twitches of the lip and fingers; case K showed eye-blinks, lip-curling and eyebrow-raising.

More complex movements intruding into both spontaneous behaviour and the performance of elicited motor tasks were noted in 10 patients. Four patients (cases D, K, P and Q) when requested to perform a rapid alternating pronation-supination movement of one hand on the back of the other stationary hand, showed 'parasitic' mirror-movements of the contralateral hand. Three patients (cases I, K and M) showed unnaturally obvious adventitious head-nodding and/or arm and shoulder movements during the performance of rapid alternating upper limb motor tasks. Other 'manneristic' and 'tic-like ' movements included, for example, tapping flanks with both hands before standing on one leg, and tapping or stamping on the floor with one foot before walking (case A); tongue-protrusion and slow facial grimacing while writing (case G); repetitive head-touching, eye-rubbing and self-grooming (case B); repetitive face-touching (case E); repetitive touching of the floor and repetitive nose-touching (case P). Three patients (cases A, B and E) showed a general fidgetiness and restlessness of the whole body, case A frequently punching the furniture during examination.

Two patients displayed abnormal postures of head and neck or limbs; in case E the right arm was held hyper-pronated during walking, with the head and neck tilted and rotated to the right; in case A the right arm was habitually hyper-supinated with the right hand making constant, slow 'kneading' movements.

Case K showed a mild dyspraxia when requested to demonstrate how to strike a match, hammer a nail, or comb hair. Case Q mimicked, unsolicited, some movements and gestures of the examiner. Case Q showed perseveration of elicited hand-movements during examination of the upper limbs.

Among the controls, there were few additional abnormal neurological findings. One subject showed rhythmic head-nodding during examination of rapid alternating movements of the upper limbs together with adventitious movements of the left hand when performing tongue movements. Two subjects showed mirror movements of the static right fist when executing rapid supination-pronation movements with the left hand. One subject performed alternating movements of the upper limbs with unusual rapidity. An examination for upper limb asynkinesia was not performed in the controls, but none of the other abnormalities found in the patients was revealed.

Neuropsychology

One patient (case N) refused to undergo psychological testing. Scores obtained in each test by the control and patient groups, together with their statistical comparison, are summarized in Table 4. A reanalysis after excluding the 6 cases as described above is also shown in Table 4, and the significant differences between patients and controls remain.

Individual test results in the patient group are summarized in Table 5. Cases are scored as positive if the result achieved in each test is poorer than the control group mean by

TABLE 4 NEUROPSYCHOLOGY TEST SCORES

Mean ± SD in controls (n = 15) and slow patients[1]

Test	*Controls*	*A*	P^2	[*B*	P^2]
NART	114.2±7.66	114.6 ±8.45	n s	[113.5 ±7.87	n.s.]
LOT	26.5±4.23	25 5 ±4.75	n s	[25.5 ±5.59	n.s.]
BD	11.3±3.07	8.0 ±3.2	0 005	[8 27±3 64	0.025]
WCST					
Errors	4.3±6.84	12.8 ±10 41	0.01	[12.82±10 46	0.025]
Perseveration (Nelson)	0.8±1.11	2 81±2 57	0.005	[2.55±2.42	0 025]
Perseveration (Milner)	0 7±0.68	3 63±3 85	0.005	[3 55±4.30	0.025]
Categories	6.6±1 25	4.19±1 56	0.0005	[4.00±1.67	0.0005]
WF type 1					
Totals	53.3±12.4	38.31±14.81	0 005	[42.45±13.37	0 025]
Perseveration	0.3±0.6	1.69±2 21	0 025	[2 27±2 45	0.01]
WF type 2					
Totals	18.9±3.0	14 88±3.95	0.005	[15.55±3.11	0.01]
Perseveration	0.4±0.88	1.19±1 80	n s.	[1 09±1.81	n s]
MRMT					
Total errors	2.3±2 41	6.19±5.75	0 025	[5.73±5.61	0 05]
SPOT					
Total errors	1 47±1 59	8.38±7 54	0 005	[8.45±8 20	0.01]
SMT					
Total errors	58.6±23.74	91 44±46.71	0.025	[98.00±47.28	0.01]
Rule breaks	4.7±9.41	12.38±11.60	0.05	[13.09±12.49	0.05]
No. of trials	9.2±1.15	9.19±1.72	n.s.	[9 27±1.79	n.s.]

[1] Column A shows the means ± SDs for the whole group of slow patients except subject N who refused to participate (n = 16). Column B in brackets shows the means ± SDs for the patient group after removal of cases F, H, J, L and O (n = 11)—for explanation, *see* Results section. [2] Comparison of control and patient groups showing significance level for a one-tailed *t*-test. n.s. = not significant.

TABLE 5 NEUROPSYCHOLOGY INDIVIDUAL TEST SCORES

	Case code[1]																
Test	*A*	*B*	*C*	*D*	*E*	*F*	*G*	*H*	*I*	*J*	*K*	*L*	*M*	*O*	*P*	*Q*	
LOT			+														(6)[2]
BD	+	+	+		+	+											(31)
WCST																	
Errors	+		+			+	+										(25)
Perseveration (Nelson)	+		+					+					+	+	+		(38)
Perseveration (Milner)	+		+					+		+			+	+		+	(44)
Categories	+	+	+		+	+	+	+					+	+		+	(63)
WF type 1																	
Totals			+			+		+				+					(25)
Perseveration	+		+		+				+		+				+	+	(44)
WF type 2																	
Totals			+			+		+			+						(25)
Perseveration										+				+	+		(19)
MRMT																	
Total errors	+	+	+	+		+											(31)
SPOT																	
Total errors	+	+	+			+	+	+		+		+	+			+	(63)
SMT																	
Total errors	+		+				+				+	+	+				(38)
Rule breaks							+					+	+				(19)
No. of trials																	(0)
	9[3]	4	12	1	3	7	5	6	1	3	3	4	6	4	3	4	

+ = scored more poorly than 2 SDs from the control mean [1]Subject N refused to participate. [2]Numbers in parentheses show the percentage of the group performing more poorly than 2 SDs from the control mean. [3]Numbers show the 'Neuropsychological Impairment Score' for each case (*see text*)

2 or more standard deviations, representing a score held by less than 2.5% of the normal control population. Using this criterion, the poorest performance in the patient group was obtained on the Wisconsin card sorting test. Ten patients (63%) achieved only 1–4 categories (control mean 6.6). Using Milner's classification, 7 patients (44%) made 3–11 perseverations (control mean 0.7); using Nelson's classification, 6 patients (38%) made 4–8 perseverations (control mean 0.8); 4 patients (25%) made 22–34 errors in the test (control mean 4.3).

Poor performance was also obtained in the Semmes personal orientation test. Ten patients (63%) made 5–23 errors (control mean 1.47).

In the word fluency test (Type 1) 7 patients (44%) made 2–9 perseverations (control mean 0.3), and 4 patients (25%) generated only 17–23 words (control mean 53.3). In the word fluency test (Type 2) 3 patients (19%) made 3–6 perseverations (control mean 0.4), and 4 patients (25%) generated only 8–12 words (control mean 18.9).

In the block design subtest of the WAIS, 5 patients (31%) scored only 4–5 (control mean 11.3). In the money road map test 5 patients (31%) made 9–18 errors (control mean 2.3). Finally, in the stylus maze test, 6 patients (38%) made 109–179 errors (control mean 58.6), and 3 patients (19%) made 27–36 rule breaks (control mean 4.7). However, patients and controls required a comparable number of trials to complete the test (control mean 9.2).

Inter-relationships of data

Because of the large amount of data collected from a relatively small and probably heterogeneous patient group, it was felt wise to restrict any further data analysis to that of testing the small number of hypotheses which had seemed clinically relevant at the outset of the study. All hypotheses were tested using a one-tailed Spearman's rank order correlation coefficient. It was predicted that: (1) those patients showing the greatest neuromotor impairment would also show the greatest neuropsychological impairment; (2) any neuromotor impairment or subjective measure of slowness would not simply be a reflection of depressive psychomotor retardation; (3) any neuropsychological impairment would similarly be unrelated to a measure of depression; (4) the slowness questionnaire would receive some independent validation from measures of neuromotor and neuropsychological impairment; (5) the greatest neuromotor impairment would be shown by patients scoring the most highly on measures of obsessionality.

A score expressing neuropsychological impairment was derived for each case by summing the number of tests in which a value greater than 2 SDs from the control mean had been obtained (*see* Table 9). These were not significantly correlated with the total motor scores (*see* Table 3) ($r_s = 0.118$, n.s.).

The total motor scores were significantly *negatively* correlated with the total Beck depression scores ($r_s = -0.547$, $P < 0.025$). The slowness questionnaire scores and the Beck depression scores were not significantly correlated ($r_s = -0.116$, n.s.).

The scores for neuropsychological impairment were not significantly correlated with scores on the Beck depression inventory ($r_s = -0.131$, n.s.).

The scores on the slowness questionnaire were not significantly correlated with the total motor scores ($r_s = 0.152$, n.s.); neither were they with the neuropsychological impairment scores ($r_s = -0.272$, n.s.).

Finally, although the group of slow patients in comparison with the non-slow group had shown significantly greater scores on several of the measures of obsessionality (*see* Table 1), correlation of total motor scores and Leyton symptom scores was not significant ($r_s = -0.296$, n.s.). There was a significant *negative* correlation between total motor scores and total obsessionality scores of the Maudsley obsessional-compulsive inventory ($r_s = -0.536$, $P < 0.025$).

DISCUSSION

The patient group

Marked subjective slowness as defined by the study was a feature in 17 (29%) of this consecutive series of 59 adult patients with OCD and was therefore common. The slow patients had higher scores on measures of obsessionality than those who were not slow, but they were similar in sex-distribution and age. Regarding the prevalence of depression, in the majority of cases their scores on the BDI probably indicated a degree of 'dysphoria' very commonly seen in OCD and evident on examination of our patients, though caution should be exercised in making diagnostic inferences from scores on the BDI and it was of note that the case who scored a total of 44 on this inventory showed no evidence of major depression on examination (Kendall, 1987). Comparison of birth histories in the slow patients and normal controls does not support the notion that abnormal births are unduly represented in OCD (Capstick and Seldrup, 1977). The absence of any earlier history of cerebral insult in these patients also contrasts with the finding of a greater incidence of past neurological disorder such as Sydenham's chorea, infantile epilepsy and encephalitis, in OCD as compared with non-obsessional neurosis (Grimshaw, 1964).

These patients reported slowness, sometimes amounting to hours, in completing ordinary tasks such as using the toilet, dressing, eating a meal, using taps or switches or attending to their personal hygiene. In most cases their disorder was chronic and was associated with severe personal and social handicaps; for example, none was in employment, and only 2 enjoyed close, personal relationships with people other than their blood-relatives. However, despite the severity of their difficulties, the psychiatric features were typical of the syndrome and resembled previous descriptions (Dowson, 1977; Stern and Cobb, 1978; Rasmussen and Tsuang, 1986).

Many of our slow cases resembled those reported by Rachman (1974) as suffering from 'primary obsessional slowness' and were as severely handicapped. The meticulous concern to do things properly, the periods of motionlessness and slow motion of the limbs, the breakdown into, and protraction of, component movements in ordinary behaviours such as brushing the teeth, were displayed by several patients.

Abnormalities on motor examination and other neurological findings

Interpretation of our findings should be tempered by the knowledge that the assessments were not carried out blind to the clinical status of the subject. However, although direct comparisons with other reports of neuromotor abnormality in psychiatric patients and normal controls are hampered by the different examinations used, nevertheless an impression is given that such abnormality was probably neither grossly underestimated in the controls nor grossly overestimated in the patients. In a recent blind and controlled study by Hollander *et al.* (1990), for example, in which 41 out-patients with OCD, of comparable mean age and sex-distribution to the present slow group, were compared neurologically with 20 normal controls, one category of the examination referred to as 'coordination' comprised combined ratings for a number of assessments of coordination of upper limb, lower limb, whole body movements, gait and speech. Abnormality was detected in 34 patients (83%) and 9 controls (45%). In the present study the prevalences of somewhat similar abnormalities in patients (94%) and controls (44%) were comparable.

There have been few other systematic studies of motor performance in patients with OCD. However, the kinds of neurological abnormality reported in the present study are consistent with previous uncontrolled findings and anecdotal case-reports. Schilder (1938) thought that motor disorder in routine cases of obsessional neurosis was common and felt that in about a third of cases abnormalities of, for example, postural control, tone, gait, spontaneous movement, speech and eye movement could be detected. Vujić

(1950, 1952) concurred and supplemented Schilder's findings with further observations of abnormality in facial movement, arm and hand posture, and gait. Behar *et al.* (1984) reported neuro-developmental anomalies of tone, posture and reflex in 5 out of 7 adolescents with OCD. Denckla (1989), in an uncontrolled study of 54 children and adolescents with OCD, reported neurological abnormality in 44 patients (81%). In 13 (24%), 'choreiform' movements were observed, and miscellaneous neuro-developmental abnormalities in 24%. Comparing 16 patients with Gilles de la Tourette syndrome, 16 with OCD and 16 normal subjects, Pitman (1987) reported tics in 6 (38%) of the patients with OCD and 1 (6%) normal control. Tics in the obsessional group were similar to those seen in the Gilles de la Tourette group.

More extensive observations in the literature have been made concerning the converse phenomenon of obsessive-compulsive psychopathology occurring in movement disorders. Such psychopathology was often reported in association with post-encephalitic parkinsonism, especially in association with oculo-gyric crises (Claude *et al.*, 1927; Courtney, 1928; Delbeke and Van Bogaert, 1928; McGowan and Cook, 1928; Jelliffe, 1929, 1932; Bromberg, 1930; von Economo, 1931; Steck, 1931; Lewis, 1936; Wexberg, 1937; Brickner *et al.*, 1940; Rosner, 1942; Shaskan *et al.*, 1942; Fairweather, 1947; Schwab *et al.*, 1951; Ajuriaguerra, 1971).

Soon after Gilles de la Tourette's original description of his syndrome, Guinon (1886) drew attention to its obsessive-compulsive aspects. Subsequent descriptions of the syndrome, including a further report by Gilles de la Tourette (1889) in which he revised his earlier view that the mental state in the disorder was normal, continued to pay attention to this association (Grasset, 1890; Meige, 1905; Wilson, 1927; Creak and Guttman, 1935; Wexberg, 1938). More recent research has suggested a prevalence of obsessive-compulsive phenomena in the syndrome of up to 90%, many authors stressing the similarity in form of the psychopathology in both syndromes (Fernando, 1967; Corbett *et al.*, 1969; Morphew and Sim, 1969; Montgomery *et al.*, 1982; Nee *et al.*, 1982; Frankel *et al.*, 1986; Robertson *et al.*, 1988). Other work has suggested a genetic relationship between Gilles de la Tourette syndrome and OCD (Pauls *et al.*, 1986; Comings and Comings, 1987; Pitman *et al.*, 1987).

There have been many anecdotal reports of the occurrence of obsessive-compulsive premorbid personality traits in idiopathic Parkinson's disease (Todes and Lees, 1985). In one controlled study of 30 cases, Mouren *et al.* (1983) found 'meticulousness and perfectionism' in 77% and an 'obsessional tendency towards orderliness' in 37%.

A study by Swedo *et al.* (1989*a*) comparing 23 patients with Sydenham's chorea and 14 patients with rheumatic fever but no chorea found a significantly greater incidence of obsessive-compulsive phenomena, as judged by the Leyton obsessional inventory, in the choreic group.

Abnormalities in our slow patients were often striking. They were also widespread, and by no means confined to the 4 patients carrying an additional 'neurological' diagnosis, or the 2 patients taking neuroleptics. Such abnormalities revealed by structured examination were similar to some of the signs considered inherent to the neurological syndromes referred to above. For example, poverty of spontaneous movement, flexed posture, reduced facial mobility and loss of arm-swing considered characteristic of parkinsonian syndromes were often observed. Other cases also showed difficulties of initiation of movement and loss of fluency reminiscent of parkinsonian syndromes, though decay of speed or amplitude of movement, reduced pace-length, micrographia and coarse rest tremor were not observed.

It was not only with the structured examination of elicited movement that similarities with parkinsonian syndromes were observed, but also from observation of spontaneous motor difficulty at a more 'behavioural' level as they went about their ordinary lives. The hesitations and ritualism often seen in simple actions such as picking up a cup, or the disintegration of complex sequences of action involved in, for example, brushing the teeth, putting on clothes, etc., into component movements that are then carried out serially with slow and careful deliberation, have been commented on in Parkinson's disease (Schwab *et al.*, 1954). The common difficulty negotiating obstacles in the environment such as doorways, the hesitations, blockings, and episodes of 'freezing' and of slow motion, hint at the kind of perceptual-motor dysfunctions some associate with the syndrome (Stern, 1983).

In a study of 90 patients with Gilles de la Tourette syndrome, Robertson *et al.* (1988) report a variety of simple and complex adventitious movements similar to those found in our patients, even after exclusion of those 2 cases carrying this additional diagnosis. For example, some or all of such features as facial grimacing, nasal twitching, lip curling, eyebrow raising and jerking and twitching of the arms were seen in 3 cases. Repetitive touching of objects or the self was seen in a further 3 cases.

No subject was suffering from major depression at the time of assessment, and our failure to demonstrate any positive correlation between scores on the slowness questionnaire or total motor score and the Beck depression inventory support our impression that slowness and motor impairment were not reflections of depressive psychomotor retardation. The negative correlation between the total motor score and both the Beck depression inventory and the Maudsley obsessional-compulsive inventory measure of obsessionality was intriguing. We have no means of knowing from this cross-sectional study when motor dysfunction developed in the course of these patients' psychiatric disorder. However, it was of interest that case D, in whom Parkinson's disease appeared after many years of classical obsessive-compulsive difficulties, reported a lessening of her obsessionality after the onset of this hypokinetic movement disorder. Similarly, the suppression with neuroleptic drugs of the 'positive' psychiatric symptoms of many forms of acute mental illness appears related to the development of a similar motor syndrome. Further, Robertson and colleagues' study of the psychopathology of Gilles de la Tourette syndrome (Robertson *et al.*, 1988) found that those patients being treated with neuroleptics had lower scores on measures of obsessionality, though whether there was an increased prevalence of parkinsonian features in this subgroup was not examined. In contrast, there is some evidence that, in patients with Gilles de la Tourette syndrome who show features of OCD, the hyperkinetic aspects of the motor disorder may antedate the development of OCD by many years (Pauls *et al.*, 1986; Pitman *et al.*, 1987).

The lack of a positive correlation between total motor score, which predominantly reflects slowness and coordination of elicited fine movement, and measures of obsessionality suggests that the findings in the structured motor examination are not specific to OCD. Indeed, evidence has accumulated that such motor deficits are common to a number of other idiopathic psychiatric syndromes such as the schizophrenias (Kennard, 1960; Hertzig and Birch, 1966; Tucker *et al.*, 1975; Quitkin *et al.*, 1976;

Manschreck *et al.*, 1982; Nasrallah *et al.*, 1982; Owens *et al.*, 1982; Manschreck and Ames, 1984; Rogers, 1985), the affective psychoses (Manschreck and Ames, 1984), the schizoaffective psychoses (Walker, 1981) and character disorders (Quitkin *et al.*, 1976).

The lack of positive correlation between scores on the slowness questionnaire and total motor score also suggests that these patients' subjective slowness was not accounted for simply by the difficulties demonstrated by the structured examination of elicited movement. Observation of these patients in fact suggested that in many the delay shown in the completion of ordinary tasks reflected the intrusion into their behaviour of unwanted and time-consuming perseverative movements, or *rituals*.

Neuropsychological abnormalities

The patients were of above average IQ as judged by the National Adult Reading Test, yet their performance was clearly differentiated from that of the normal controls, and impairment on the tests employed was widespread. Reanalysis omitting those 6 cases with either additional 'neurological' diagnoses or on neuroleptics did not alter this conclusion. The lack of positive correlations between neuropsychological impairment score and BDI or slowness questionnaire scores suggest that performance on these tests was a reflection neither of depression nor of slowness. Furthermore, time constraints were disregarded in all but one test (verbal performance). Non-specific difficulties in attention, memory or concentration also fail to account satisfactorily for their impaired performance as, within individuals, impairment across the tests was not uniform. Furthermore, as a group, the number of trials required to learn the stylus maze test and, with one exception, performance in the line orientation test, were normal.

Our findings replicate some aspects of previous studies of neuropsychological impairment in OCD. Three studies have used the Money road map test and suggested deficits in comparison with normal controls (Behar *et al.*, 1984; Cox *et al.*, 1989; Head *et al.*, 1989). Three studies have used the stylus maze test: Head *et al.* (1989) failing to find the deficits reported by Behar *et al.* (1984) and Cox *et al.* (1989). Two studies have employed the Wisconsin card sorting test and found impairment in comparison with normal controls (Cox *et al.*, 1989; Head *et al.*, 1989). Four studies have employed the block design subtest of the Wechsler adult intelligence scale (Rapoport *et al.*, 1981; Insel *et al.*, 1983; Behar *et al.*, 1984; Head *et al.*, 1989) only Head *et al.* (1989) demonstrating any impairment in comparison with normal controls. Head *et al.* (1989) found lower word fluency totals in comparison with normal controls, though no increase in perseveration, and normal performance in the line orientation test and personal orientation test.

The tests used in our patients were selected not only because they have previously demonstrated impairment in studies of patients with Parkinson's disease and so-called frontal lobe disorders (*see* Introduction), but also because they appeared possibly to reflect 3 distinct but related cognitive functions: firstly, pure spatial ability; secondly, cognitive set-switching ability and thirdly, a mixture of set-switching and spatial ability (Head *et al.*, 1989). The line orientation test is perhaps the purest test of spatial ability (Benton *et al.*, 1978). Although the block design relies heavily on spatial ability it also perhaps requires other more complex thinking processes (De Renzi, 1982) and is, therefore, less pure. Poor performance is said to correlate especially with right parietal dysfunction. Wisconsin card sorting test and word fluency both require systematic and repeated shifts of non-spatial response category with scoring of perseverative error and were, therefore, regarded as relatively pure tests of set-shifting ability. The Money road map test and personal orientation test appeared to require a mixture of spatial and shifting abilities in that they demand repeated and systematic changes of mental spatial perspective. The stylus maze test involves learning a spatial arrangement through constant shifting of visual-motor responses to environmental cues and also, therefore, seems to demand both spatial and shifting abilities.

Our results suggest that pure spatial ability as judged by the line orientation test is relatively intact in our patients, whilst set-shifting ability and complex spatial-and-shifting abilities are impaired compared with normal controls. Comparison with the study by Head *et al.* (1989) shows a similar preservation of pure spatial judgement in our patients but a more uniform and widespread impairment in the other tests. The patients studied by Head *et al.* (1989), and patients in the other 4 studies, were not selected because of severe slowness, and although neither slowness questionnaire nor obsessionality scores were positively correlated with neuropsychological impairment, it seems likely that our patients were more severely handicapped by their disorder and that this might be expected to be reflected in more pervasive neuropsychological difficulties.

The Wisconsin card sorting test, Money road map test, personal orientation test, stylus maze test and word fluency tests have all been reported to be sensitive to 'frontal lobe' impairment in comparison with patients with damage in other regions of the brain or with normal controls (Semmes *et al.*, 1963; Milner, 1964; Teuber, 1964; Benton, 1968; Butters *et al.*, 1972). Poor performance in the Wisconsin card sorting test, a route walking test similar to the Money road map test, the personal orientation test and word fluency tests, has also been reported in patients with Parkinson's disease (Bowen *et al.*, 1972, 1976; Bowen, 1976; Lees and Smith, 1983; Taylor *et al.*, 1986).

The fact that neuropsychological impairment scores were not positively correlated either with measures of obsessionality or with the total motor score suggests, as with motor function, that the neuropsychological findings might not necessarily be specific to OCD or to the patterns of motor dysfunction observed in these patients. Certainly, similar neuropsychological deficits have frequently been commented upon in other idiopathic psychiatric syndromes such as the schizophrenias (Fey, 1951; Malmo, 1974; Levin, 1984; Weinberger *et al.*, 1986; Goldberg *et al.*, 1987).

Anatomical considerations and recent neuro-imaging studies in OCD

Although the functions of the frontal cortex in man are very imperfectly understood, there is, nevertheless, general agreement that this area of the brain is one which is intimately concerned in the initiation and regulation of complex, non-reflexive motor-programmes (Teuber, 1964, 1966; Nauta, 1971; Luria 1976). Patients and experimental animals with frontal lobe dysfunction typically display a disruption of goal-directed behaviour whose features include a defective initiation and stability of action, the occurrence of rigid stereotypies, perseveration, an excessive vulnerability to interfering events and, in man, an imperviousness to self-directed verbal commands.

The clinical psychiatric features of all of our obsessionally slow patients are strongly reminiscent of frontal lobe/basal ganglia deficits of behavioural and motor programming. Indeed, the inefficacy of verbal control over self-directed perseverative action or 'ritual'

TABLE 6 NEURO-IMAGING STUDIES IN OCD· SINGLE CASE-REPORTS

Reference	*Case details (age, sex/diagnosis/OCD/CNS)*[1]	*Imaging*[2]
Laplane *et al* (1981)	Male, aged 53/Wasp sting encephalopathy/ Compulsive counting and finger movements/Facial and finger tic-like movements; choreiform and parkinsonian gait	*CT*: low densities in lentiform and caudate nuclei bilaterally and R putamen
Laplane *et al* (1982)	Male, aged 23/CO poisoning/Compulsive counting/Normal	*CT*: low density in lentiform nuclei bilaterally *PET*. bilateral medio-frontal and L latero-frontal hypometab , latero-occipital hypermetab.
Ali-Cherif *et al* (1984)	Male, aged 46/CO poisoning/Compulsive coprolalia/Normal	*CT*: bilat. hypodensity of globus pallidus slight cortical and ventricular atrophy
Ali-Cherif *et al.* (1984)	Female, aged 20/CO poisoning/Obsessional tidiness/hoarding/Normal	*CT*: bilat hypodensity of globus pallidus
Paunovic (1984)	Male, aged 45/Cerebral thrombosis/ Obessional ruminations/slight pyramidal weakness R arm and face	*Radio scan*. L frontal hypoperfusion
Eslinger and Damasio (1985)	Male, aged 35/Frontal ablation/Obsessional indecision, hoarding, slowness/Normal	*CT, NMR and SPET*: bilat. orbital and medial frontal lesions
Laplane *et al.* (1988*a*)	Female, aged 31/CO poisoning/Compulsive counting and verbal repetition, obsessional ruminations/General slowing	*CT and NMR*: bilateral lesions of lentiform nuclei and globus pallidus *PET* medio- and latero-frontal, and R striatal hypometabolism
Laplane *et al* (1988*b*)	Female, aged 59/Head injury/Compulsive counting/General inertia	*CT and NMR*. bilat frontal lesions L > R ventricular enlargement *PET*. bilat frontal hypometabolism
Williams *et al* (1988)	Female, aged 48/? Ischaemia/Compulsive finger movements/Normal	*CT*: bilat. cavitation of caudate and R putamen
Ward (1988)	Female, aged 59/Glioma/Urge to walk to L/Mild L hemiparesis	*CT* R fronto-parietal glioma
Ward (1988)	Male, aged 43/Glioma/Urge to shout and move R arm/Mild R hemiparesis, expressive dysphasia, papilloedema	*CT*: L frontal glioma
Ward (1988)	Female, aged 62/? Ischaemia/Urge to shake R arm/Normal	*CT*: ? infarcts in L basal ganglia, R cerebellum
Laplane *et al* (1989)	Female, aged 27/Cerebral anoxia/ Obessional routines and compulsive repetitive action; marked slowness/Tremor, rigidity, pyramidal syndrome 'all improved'	*CT and NMR*: small bilateral lesions in lentiform nuclei *PET*: bilateral hypometabolism in striatum and L latero-frontal
Laplane *et al.* (1989)	Male, aged ?/Cerebral anoxia/Compulsive checking, touching and repetition of action, number rituals/Normal	*NMR*: bilateral lesions in globus pallidus lentiform and putamen *PET* R striatal hypometabolism
Weilburg *et al* (1989)	Male, aged 24/? Perinatal anoxia/Repetitive washing, checking, ruminations/Abnormal posture and hypertonia R arm	*CT*: prominent temporal horns and asymmetry of frontal horns; hypodensity L caudate head and ? putamen *NMR*: enlarged anterior L lateral ventricle and loss of volume of L caudate head and putamen

[1] OCD = obsessive-compulsive features, CNS = findings on neurological examination [2] CT = computerized tomography, NMR = nuclear magnetic resonance; PET = positron emission tomography.

is a cardinal experiential and behavioural feature of the syndrome of OCD. The 'forced attention' or 'forced avoidance' of environmental sensory stimuli which were prominent in several of our patients (*see* Table 3) are, furthermore, reminiscent of Denny-Brown's 'magnetic' and 'repellent' apraxias, in which he believed different degrees of inhibition or release of frontal mechanisms to be operating (Denny-Brown, 1958). The clinical features of our patients and of OCD in general, therefore, suggest that disruption of brain functions subserved by frontal and basal ganglia structures could be of crucial importance.

In 1981, Laplane *et al.* reported a patient who demonstrated obsessive-compulsive behaviour and motor slowness in association with structural lesions of the basal ganglia as revealed by CT scanning (Laplane *et al.*, 1981, 1989). Since then, using CT, MRI or PET-scanning techniques, several further single case-reports have been published of patients in whom there has been a conjunction of obsessive-compulsive phenomena and structural and physiological disturbances of frontal cortex and basal ganglia. These case-reports are summarized in Table 6. The presence of their cerebral abnormalities was an important selection criterion in the reporting of these patients and, as such, they may represent a very unusual psychiatric population. However, using similar imaging techniques, several systematic studies of patients with OCD who were not selected because

TABLE 7 NEURO-IMAGING STUDIES IN OCD GROUP STUDIES

Reference	*Details of subjects*[1]	*Imaging*[2]
Baxter *et al.* (1987)	14 OCD (35 ± 12 yrs) vs 14 depressed (35 ± 12 yrs) and 14 normal controls (32 ± 5 yrs)	*PET*: absolute and hypermetabolism of both heads of caudate and L orbital gyrus in OCD vs both control groups; overlap of L orbital gyrus/ipsilateral hemisphere ratios in OCD and depressed vs normal; elevated caudate/ipsilateral hemisphere ratio in OCD treatment responders vs non-responders
Luxenburg *et al* (1988)	10 male severe OCD (21 ± 2 yrs) vs 10 normal male controls (24 ± 3 yrs)	*CT*. reduced caudate volume bilaterally
Baxter *et al.* (1988)	10 OCD (36 ± 11 yrs) vs 10 normal controls (40 ± 12 yrs)	*PET*: absolute hypermetabolism bilaterally in caudate heads, orbital gyri and whole hemispheres, bilaterally raised orbital gyrus/ipsilateral hemisphere ratios
Garber *et al.* (1989)	32 OCD (35 ± 9 yrs) vs 14 normal controls (34 ± 10 yrs)	*NMR*: R frontal prolonged T_1; greater R-minus-L T_1 frontal white matter differences in OCD, no structural abnormalities demonstrated
Nordahl *et al.* (1989)	8 OCD (33 ± 6 yrs) vs 30 normal controls (36 ± 11 yrs) during a continuous auditory discrimination task	*PET*: normal global metabolic rates; raised orbital frontal/global ratios bilaterally; normal caudate and putamen; possibly hypometabolic R parietal and L parieto-occipital cortex?
Swedo *et al.* (1989*b*)	18 OCD of childhood onset (28 ± 7 yrs) vs 18 normal controls (32 ± 7 yrs	*PET*: normal global metabolic rates; raised R prefrontal/global and L anterior cingulate/global ratios; normal caudate and lentiform nuclei; some correlations between metabolic measures and state and trait features and response to drug treatment

[1] OCD = obsessive-compulsive disorder; figures in parentheses give mean ages of groups ± their standard deviations

[2] PET = positron emission tomography, NMR = nuclear magnetic resonance; CT = computerized tomography; R = right, L = left

of the presence of neurological abnormality, either clinically or on investigation, have recently appeared and show a compelling anatomical congruence with the case reports, and a striking anatomical consistency with each other. The findings of these studies which point particularly to dysfunctions of frontal cortex are summarized in Table 7.

Conclusions

Marked subjective slowness and delay in the execution of the ordinary tasks of living was a common feature in an unselected group of patients with severe OCD. Such complaints appeared to derive principally from difficulties in initiating goal-directed action, and from difficulties in suppressing perseverative behaviours during the course of such action. Further structured examination of these patients revealed a number of motor and cognitive impairments consistent with the hypothesis that functions served by frontal and basal ganglia mechanisms might be impaired. Recent neuro-imaging studies provide some support for this notion.

The motor abnormalities and other neurological findings are so-called 'soft neurological signs'. OCD is likely to be as biologically heterogeneous as other major psychiatric syndromes (Mapother, 1933) and future studies might usefully examine populations unselected for slowness in an attempt to establish homogeneous groups defined by their behavioural neurological characteristics and the presence and pattern of such soft-signs. Investigation of such groups with recent neuro-imaging techniques may begin to provide validation for such an approach.

Despite the fact that the clinical neurological findings in our patients were widespread and elicited with reasonable reliability, most patients had normal physical examinations recorded in their admission notes. Physical examination, especially of the neuromotor system, is often neglected by psychiatrists (Rigby and Oswald, 1987). This may reflect psychiatrists' lack of confidence in the required neurological skills (McIntyre and Romano, 1977) or it may reflect a lack of interest in the neurological dimensions of psychiatric illness (Rogers, 1985). Whatever the reason, Janet's caveat that the mental state of obsessional patients should not distract one from a physical examination (Janet, 1903) becomes increasingly relevant as the technologies of neurology and psychiatry converge (Stevens, 1982; Caine and Joynt, 1986).

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REFERENCES

AJURIAGUERRA J DE (1971) Étude psychopathologique des parkinsoniens. In. *Monoamines, Noyaux Gris Centraux et Syndrome de Parkinson.* Edited by J. de Ajuriaguerra and G. Gauthier. Geneva: Georg, pp. 327–351.

ALI-CHERIF A, ROYERE ML, GOSSET A, PONCET M, SALAMON G, KHALIL R (1984) Troubles du comportement et de l'activité mentale après intoxication oxycarbonée. *Revue Neurologique,* **140,** 401–405.

American Psychiatric Association (1980) *Diagnostic and Statistical Manual of Mental Disorders, DSM-III.* Third edition Washington, DC: American Psychiatric Association.

Baxter LR, Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE (1987) Local cerebral glucose metabolic rates in obsessive-compulsive disorder: a comparison with rates in unipolar depression and in normal controls. *Archives of General Psychiatry,* **44,** 211–218.

Baxter LR, Schwartz JM, Mazziotta JC, Phelps ME, Pahl JJ, Guze BH *et al.* (1988) Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *American Journal of Psychiatry,* **145,** 1560–1563.

Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J (1961) An inventory for measuring depression. *Archives of General Psychiatry,* **4,** 561–571.

Behar D, Rapoport JL, Beg CJ, Denckla MB, Mann L, Cox C *et al.* (1984) Computerized tomography and neuropsychological test meaures in adolescents with obsessive-compulsive disorder. *American Journal of Psychiatry,* **141,** 363–369.

Benton AL (1968) Differential behavioral effects in frontal lobe disease. *Neuropsychologia,* **6,** 53–60.

Benton AL (1976) The measurement of aphasic disorders. In: *Neuropsychological Assessment.* Edited by M. D. Lezak. New York: Oxford University Press.

Benton AL, Varney NR, Hamsher KS (1978) Visuospatial judgment: a clinical test. *Archives of Neurology, Chicago,* **35,** 364–367.

Berrios GE (1985) Obsessional disorders during the nineteenth century: terminological and classificatory issues. In: *The Anatomy of Madness. Essays in the History of Psychiatry,* Volume 1. Edited by W. F. Bynum, R Porter and M. Shepherd. London: Tavistock, pp. 166–187.

Borkowski JG, Benton AL, Spreen O (1967) Word fluency and brain damage. *Neuropsychologia,* **5,** 135–140.

Bowen FP (1976) Behavioral alterations in patients with basal ganglia lesions. *Research Publications· Association for Research in Nervous and Mental Disease,* **55,** 169–180.

Bowen FP, Hoehn MM, Yahr MD (1972) Parkinsonism: alterations in spatial orientation as determined by a route-walking test. *Neuropsychologia,* **10,** 355–361.

Bowen FP, Burns MM, Brady EM, Yahr MD (1976) A note on alterations of personal orientation in parkinsonism. *Neuropsychologia,* **14,** 425–429.

Brickner RM, Rosner AA, Monro R (1940) Physiological aspects of the obsessive state. *Psychosomatic Medicine,* **2,** 369–383.

Bromberg W (1930) Mental states in chronic encephalitis. *Psychiatric Quarterly,* **4,** 537–566.

Butters N, Soeldner C, Fedio P (1972) Comparison of parietal and frontal lobe spatial deficits in man: extrapersonal vs. personal (egocentric) space. *Perceptual and Motor Skills,* **34,** 27–34.

Bynum WF (1985) The nervous patient in 18th and 19th century Britain: the psychiatric origins of British neurology. In. *The Anatomy of Madness—Essays in the History of Psychiatry,* Volume 1. Edited by W. F. Bynum, R. Porter and M. Shepherd. London: Tavistock, pp. 89–102.

Caine ED, Joynt RJ (1986) Neuropsychiatry . . . Again. *Archives of Neurology, Chicago,* **43,** 325–327.

Capstick N, Seldrup J (1977) Obsessional states: a study in the relationship between abnormalities occurring at the time of birth and the subsequent development of obsessional symptoms. *Acta Psychiatrica Scandinavica,* **56,** 427–431.

Claude H, Baruk H, Lamache A (1927) Obsessions-impulsions consécutives à l'encéphalite épidémique. *Encéphale,* **22,** 716–720.

Cohen J (1968) Weighted kappa: nominal scale agreement with provision for scaled disagreement or partial credit. *Psychological Bulletin,* **70,** 213–219.

Comings DE, Comings BG (1987) Hereditary agoraphobia and obsessive-compulsive behaviour in relatives of patients with Gilles de la Tourette's syndrome. *British Journal of Psychiatry,* **151,** 195–199.

Cooper J (1970) The Leyton Obsessional Inventory. *Psychological Medicine,* **1,** 48–64.

Corbett JA, Mathews AM, Connell PH, Shapiro DA (1969) Tics and Gilles de la Tourette's syndrome: a follow-up study and critical review. *British Journal of Psychiatry,* **115,** 1229–1241.

Courtney JW (1928) A case of postencephalitic parkinsonian disease, with polydipsia *Archives of Neurology and Psychiatry, Chicago,* **19,** 188–190.

Cox CS, Fedio P, Rapoport JL (1989) Neuropsychological testing of obsessive-compulsive adolescents. In: *Obsessive-Compulsive Disorder in Children and Adolescents.* Edited by J. L Rapoport. Washington: American Psychiatric Press, pp. 73–87.

CRAWFORD JR, BESSON JAO, PARKER DM, SUTHERLAND KM, KLEEN PL (1987) Estimation of premorbid intellectual status in depression. *British Journal of Clinical Psychology,* **26,** 313–314.

CRAWFORD JR, PARKER DM, BESSON JAO (1988) Estimation of premorbid intelligence in organic conditions. *British Journal of Psychiatry,* **153,** 178–181.

CREAK M, GUTTMAN E (1935) Chorea, tics and compulsive utterances. *Journal of Mental Science,* **81,** 834–839.

CUMMINGS JL, FRANKEL M (1985) Gilles de la Tourette syndrome and the neurological basis of obsessions and compulsions. *Biological Psychiatry,* **20,** 1117–1126.

DELBEKE R, BOGAERT L VAN (1928) Le problème général des crises oculogyres au cours de l'encéphalite épidémique chronique: a propos de vingt-cinq observations personelles. *Encéphale,* **23,** 855–890.

DENCKLA MB (1989) Neurological examination. In: *Obsessive Compulsive Disorder in Children and Adolescents.* Edited by J. L. Rapoport. Washington: American Psychiatric Press, pp. 107–119.

DENNY-BROWN D (1958) The nature of apraxia. *Journal of Nervous and Mental Disease,* **126,** 9–32.

DOWBIGGIN I (1985) Degeneration and hereditarianism in French mental medicine 1840–1890: psychiatric theory as ideological adaptation. In: *The Anatomy of Madness. Essays in the History of Psychiatry,* Volume 1. Edited by W. F. Bynum, R. Porter and M. Shepherd. London: Tavistock, pp. 188–232.

DOWSON JH (1977) The phenomenology of severe obsessive-compulsive neurosis. *British Journal of Psychiatry,* **131,** 75–78.

ECONOMO C VON (1931) *Encephalitis Lethargica: Its Sequelae and Treatment.* Translated by K. O. Newman London: Oxford University Press.

ESLINGER PJ, DAMASIO AR (1985) Severe disturbance of higher cognition after bilateral frontal lobe ablation: patient EVR. *Neurology, Cleveland,* **35,** 1731–1741.

ESQUIROL JED (1838) De la Monomanie. In: *Des Maladies Mentales. Considérées sous les Rapports Médical, Hygiénique et Médico-Légal,* Volume 1, Paris: Baillière, pp. 355–365.

EY H, BERNARD P, BRISSET C (1974) *Manuel de Psychiatrie.* Fourth edition. Paris: Masson.

FAIRWEATHER DS (1947) Psychiatric aspects of the post-encephalitic syndrome. *Journal of Mental Science,* **93,** 201–254.

FERNANDO SJM (1967) Gilles de la Tourette's syndrome: a report on four cases and a review of published case reports. *British Journal of Psychiatry,* **113,** 607–617.

FEY ET (1951) The performance of young schizophrenics and young normals on the Wisconsin Card Sorting Test. *Journal of Consulting Psychology,* **15,** 311–319.

FRANKEL M, CUMMINGS JL, ROBERTSON MM, TRIMBLE MR, HILL MA, BENSON DF (1986) Obsessions and compulsions in Gilles de la Tourette's syndrome. *Neurology, Cleveland,* **36,** 378–382.

GARBER HJ, ANANTH JV, CHIU LC, GRISWOLD VJ, OLDENDORF WH (1989) Nuclear magnetic resonance study of obsessive-compulsive disorder. *American Journal of Psychiatry,* **146,** 1001–1005.

GILLES DE LA TOURETTE (1889) La maladie des tics convulsifs. *Semaine Médicale,* **18,** 153–156.

GOLDBERG TE, WEINBERGER DR, BERMAN KF, PLISKIN NH, PODD MH (1987) Further evidence for dementia of the prefrontal type in schizophrenia? A controlled study of teaching the Wisconsin Card Sorting Test. *Archives of General Psychiatry,* **44,** 1008–1014.

GRANT DA, BERG EA (1948) A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card-sorting problem *Journal of Experimental Psychology,* **38,** 404–411.

GRASSET I (1890) Leçons sur un cas de maladie des tics et un cas de tremblement singulier de la tête et des membres gauches. *Archives de Neurologie,* **20,** 27–45 and 187–211.

GREENFIELD JG (1976) *Greenfield's Neuropathology.* Third edition. Edited by W. Blackwood and J. A. N. Corsellis. London: Edward Arnold.

GRIMSHAW L (1964) Obsessional disorder and neurological illness. *Journal of Neurology, Neurosurgery, and Psychiatry,* **27,** 229–231.

GUINON G (1886) Sur la maladie des tics convulsifs. *Revue de Médecine,* **6,** 50–80.

HEAD D, BOLTON D, HYMAS NFS (1989) Deficit in cognitive shifting ability in patients with obsessive-compulsive disorder. *Biological Psychiatry,* **25,** 929–937.

HERTZIG ME, BIRCH HG (1966) Neurologic organization in psychiatrically disturbed adolescent girls. *Archives of General Psychiatry,* **15,** 590–598.

HODGSON RJ, RACHMAN S (1977) Obsessional-compulsive complaints. *Behaviour Research and Therapy,* **15,** 389–395.

HOLLANDER E, SCHIFFMAN E, COHEN B, RIVERA-STEIN MA, ROSEN W, GORMAN JM *et al.* (1990) Signs of central nervous system dysfunction in obsessive-compulsive disorder. *Archives of General Psychiatry*, **47**, 27–32.

HUNTER R (1973) Psychiatry and neurology: psychosyndrome or brain disease. *Proceedings of the Royal Society of Medicine*, **66**, 359–364.

HYMAS NFS, PRASAD AJ (1989) Obsessive-compulsive disorder: its clinical neurology and recent pharmacological studies. In: *Biological Basis and Therapy of Neuroses.* Edited by A. J. Prasad. Boca Raton, FL: CRC Press, pp. 41–79.

INSEL TR, DONNELLY EF, LALAKEA ML, ALTERMAN IS, MURPHY DL (1983) Neurological and neuropsychological studies of patients with obsessive-compulsive disorder. *Biological Psychiatry*, **18**, 741–751.

JACKSON JH (1895) On imperative ideas: being a discussion on Dr. Hack Tuke's paper (Brain, 1894). *Brain*, **18**, 318–322.

JANET P (1903) *Les Obsessions et la Psychasthénie.* Paris: Alcan.

JELLIFFE SE (1929) Psychologic components in postencephalitic oculogyric crises: contribution to a genetic interpretation of compulsion phenomena. *Archives of Neurology and Psychiatry, Chicago*, **21**, 491–532.

JELLIFFE SE (1932) *Psychopathology of Forced Movements and the Oculogyric Crises of Lethargic Encephalitis.* New York: Nervous and Mental Disease Publishing Company.

KENDALL PC, HOLLON SD, BECK AT, HAMMEN CL, INGRAM RE (1987) Issues and recommendations regarding use of the Beck depression inventory. *Cognitive Therapy and Research*, **11**, 289–299.

KENNARD MA (1960) Value of equivocal signs in neurologic diagnosis. *Neurology, Minneapolis*, **10**, 753–764.

LAPLANE D, WIDLOCHER D, PILLON B, BAULAC M, BINOUX F (1981) Comportement compulsif d'allure obsessionnelle par nécrose circonscrite bilatérale pallido-striatale. encéphalopathie par piqûre de guêpe. *Revue Neurologique*, **137**, 269–276.

LAPLANE D, BAULAC M, PILLON B, PANAYOTOPOULOU-ACHIMASTOS I (1982) Perte de l'auto-activation psychique. Activité compulsive d'allure obsessionnelle. Lésion lenticulaire bilatérale. *Revue Neurologique*, **138**, 137–141.

LAPLANE D, BAULAC M, WIDLÖCHER D, DUBOIS B (1984) Pure psychic akinesia with bilateral lesions of basal ganglia. *Journal of Neurology, Neurosurgery, and Psychiatry*, **47**, 377–385.

LAPLANE D, BOULLIAT J, BARON JC, PILLON B, BAULAC M (1988*a*) Comportement compulsif d'allure obsessionelle par lésion bilatérale des noyaux lenticulaires. Un nouveau cas. *Encéphale*, **14**, 27–32

LAPLANE D, DUBOIS B, PILLON B, BAULAC M (1988*b*) Perte d'autoactivation psychique et activité mentale stéréotypée par lésion frontale: rapports avec le trouble obsessivo-compulsif. *Revue Neurologique*, **144**, 564–570.

LAPLANE D, LEVASSEUR M, PILLON B, DUBOIS B, BAULAC M, MAZOYER B *et al.* (1989) Obsessive-compulsive and other behavioural changes with bilateral basal ganglia lesions: a neuropsychological, magnetic resonance imaging and positron tomography study. *Brain*, **112**, 699–725.

LEES AJ, SMITH E (1983) Cognitive deficits in the early stages of Parkinson's disease. *Brain*, **106**, 257–270

LEVIN S (1984) Frontal lobe dysfunctions in schizophrenia. 2. Impairments of psychological and brain functions. *Journal of Psychical Research*, **18**, 57–72.

LEWIS A (1936) Problems of obsessional illness. *Proceedings of the Royal Society of Medicine*, **29**, 325–336.

LURIA AR (1976) *The Working Brain: An Introduction to Neuropsychology.* Translated by B. Haigh. London: Allen Lane.

LUXENBERG JS, SWEDO SE, FLAMENT MF, FRIEDLAND RP, RAPOPORT J, RAPOPORT SI (1988) Neuroanatomical abnormalities in obsessive-compulsive disorder detected with quantitative X-ray computed tomography. *American Journal of Psychiatry*, **145**, 1089–1093.

MCCOWAN PK, COOK LC (1928) The mental aspect of chronic epidemic encephalitis. *Lancet*, **i**, 1316–1320

MCINTYRE JS, ROMANO J (1977) Is there a stethoscope in the house (and is it used)? *Archives of General Psychiatry*, **34**, 1147–1151.

MALMO HP (1974) On frontal lobe functions: psychiatric patient controls. *Cortex*, **10**, 231–237.

MANSCHRECK TC, MAHER BA, RUCKLOS ME, VEREEN DR (1982) Disturbed voluntary motor activity in schizophrenic disorder. *Psychological Medicine*, **12**, 73–84.

MANSCHRECK TC, AMES D (1984) Neurologic features and psychopathology in schizophrenic disorders. *Biological Psychiatry*, **19**, 703–719.

MAPOTHER E (1933) Tough or tender A plea for nominalism in psychiatry. *Proceedings of the Royal Society of Medicine*, **27**, 1687–1712.

MARKS IM (1978) *Living with Fear· Understanding and Coping with Anxiety*. New York: McGraw-Hill, pp. 163–164.

MEIGE H (1905) *Tics*, Monographies Cliniques. Paris: Masson.

METCALFE M, GOLDMAN E (1965) Validation of an inventory for measuring depression. *British Journal of Psychiatry*, **111**, 240–242.

MILNER B (1963) Effects of different brain lesions on card sorting. the role of the frontal lobes. *Archives of Neurology, Chicago*, **9**, 90–100.

MILNER B (1964) Some effects of frontal lobectomy in man. In: *The Frontal Granular Cortex and Behavior* Edited by J. M. Warren and K. Akert. New York: McGraw-Hill, pp. 313–334.

MONTGOMERY MA, CLAYTON PJ, FRIEDHOFF AJ (1982) Psychiatric illness in Tourette syndrome patients and first-degree relatives. *Advances in Neurology*, **35**, 335–339.

MORPHEW JA, SIM M (1969) Gilles de la Tourette's syndrome· a clinical and psychopathological study *British Journal of Medical Psychology*, **42**, 293–301.

MOUREN P, POINSO Y, OPPENHEIM A, MOUREN A, NGUYEN QUANG M (1983) La personalité du parkinsonien—approche clinique et psychométrique. *Annales Médico-Psychologiques*, **141**, 153–167.

MURRAY RM, COOPER JE, SMITH A (1979) The Leyton Obsessional Inventory: an analysis of the responses of 73 obsessional patients. *Psychological Medicine*, **9**, 305–311.

NASRALLAH HA, TIPPIN J, MCCALLEY-WHITTERS M, KUPERMAN S (1982) Neurological differences between paranoid and nonparanoid schizophrenia: Part III. Neurological soft signs. *Journal of Clinical Psychiatry*, **43**, 310–312

NAUTA WJH (1971) The problem of the frontal lobe: a reinterpretation. *Journal of Psychiatry Research*, **8**, 167–187.

NEE LE, POLINSKY RJ, EBERT MH (1982) Tourette syndrome: clinical and family studies. *Advances in Neurology*, **35**, 291–295.

NELSON HE (1982) *National Adult Reading Test: Test Manual*. Windsor: NFER-Nelson.

NELSON HE, O'CONNELL A (1978) Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex*, **14**, 234–244.

NEWCOMBE F (1969) *Missile Wounds of the Brain: A Study of Psychological Deficits*. London: Oxford University Press.

NORDAHL TE, BENKELFAT C, SEMPLE WE, GROSS M, KING AC, COHEN RM (1989) Cerebral glucose metabolic rates in obsessive compulsive disorder. *Neuropsychopharmacology*, **2**, 23–28.

O'CARROLL RE, BAIKIE EM, WHITTICK JE (1987) Does the National Adult Reading Test hold in dementia? *British Journal of Clinical Psychology*, **26**, 315–316.

OWENS DGC, JOHNSTONE EC, FRITH CD (1982) Spontaneous involuntary disorders of movement: their prevalence, severity, and distribution in chronic schizophrenics with and without treatment with neuroleptics. *Archives of General Psychiatry*, **39**, 452–461.

PAULS DL, TOWBIN KE, LECKMAN JF, ZAHNER GEP, COHEN DJ (1986) Gilles de la Tourette's syndrome and obsessive-compulsive disorder: evidence supporting a genetic relationship. *Archives of General Psychiatry*, **43**, 1180–1182.

PAUNOVIC VR (1984) Syndrome obsessionnel au décours d'une atteinte cérébrale organique. *Annales Médico-Psychologiques*, **142**, 379–382

PITMAN R, GREEN RC, JENIKE MA, MESULAM MM (1987) Clinical comparison of Tourette's disorder and obsessive-compulsive disorder. *American Journal of Psychiatry*, **144**, 1166–1171.

QUITKIN F, RIFKIN AS, KLEIN DF (1976) Neurologic soft signs in schizophrenia and character disorders: organicity in schizophrenia with premorbid asociality and emotionally unstable character disorders. *Archives of General Psychiatry*, **33**, 845–853.

RACHMAN S (1974) Primary obsessional slowness *Behaviour Research and Therapy*, **12**, 9–18.

RADO S, MONROE RR (1974) Obsessive behavior. In: *American Handbook of Psychiatry*, Volume 3. Second edition. Edited by S. Arieti and E. B. Brody New York: Basic Books, pp. 195–223.

Rapoport J, Elkins R, Langer DH, Sceery W, Buchsbaum MS, Gillin JC *et al.* (1981) Childhood obsessive-compulsive disorder. *American Journal of Psychiatry*, **138**, 1545–1554.

Rasmussen SA, Tsuang MT (1986) Epidemiology and clinical features of obsessive-compulsive disorder. In: *Obsessive-Compulsive Disorders: Theory and Management*. Edited by M. A. Jenike, L. Baer and W. E. Minichiello. Littleton, MA: PSG Publishing Co., pp. 23–44.

Renzi E de (1982) *Disorders of Space Exploration and Cognition*. Chichester: John Wiley.

Rigby JC, Oswald AG (1987) An evaluation of the performing and recording of physical examinations by psychiatric trainees. *British Journal of Psychiatry*, **150**, 533–535.

Robertson MM, Trimble MR, Lees AJ (1988) The psychopathology of the Gilles de la Tourette syndrome: a phenomenological analysis. *British Journal of Psychiatry*, **152**, 383–390.

Rogers D (1985) The motor disorders of severe psychiatric illness: a conflict of paradigms. *British Journal of Psychiatry*, **147**, 221–232.

Rogers D (1987) Neuropsychiatry. *British Journal of Psychiatry*, **150**, 425–427.

Rosner AA (1942) Unit reaction states in oculogyric crises. *American Journal of Psychiatry*, **99**, 224–228.

Schilder P (1938) The organic background of obsessions and compulsions. *American Journal of Psychiatry*, **94**, 1397–1416.

Schwab RS, Fabing HD, Prichard JS (1951) Psychiatric symptoms and syndromes in Parkinson's disease. *American Journal of Psychiatry*, **107**, 901–907.

Schwab RS, Chafetz ME, Walker S (1954) Control of two simultaneous voluntary motor acts in normals and in parkinsonism. *Archives of Neurology and Psychiatry, Chicago*, **72**, 591–599.

Semmes J, Weinstein S, Ghent L, Teuber H-L (1963) Correlates of impaired orientation in personal and extrapersonal space. *Brain*, **86**, 747–772.

Shaskan D, Yarnell H, Alper K (1942) Physical, psychiatric and psychometric studies of post-encephalitic parkinsonism. *Journal of Nervous and Mental Diseases*, **96**, 652–662.

Slater E, Roth M (1969) *Clinical Psychiatry*. Third edition. London: Bailliere, Tindall and Cassell.

Snowdon J (1980) A comparison of written and postbox forms of the Leyton Obsessional Inventory. *Psychological Medicine*, **10**, 165–170.

Steck H (1931) Les syndromes mentaux postencéphalitiques. *Archives Suisses de Neurologie et de Psychiatrie*, **27**, 137–173.

Stern RS, Cobb JP (1978) Phenomenology of obsessive-compulsive neurosis. *British Journal of Psychiatry*, **132**, 233–239.

Stern Y (1983) Behavior and the basal ganglia. *Advances in Neurology*, **38**, 195–209.

Stevens JR (1982) The neuropathology of schizophrenia. *Psychological Medicine*, **12**, 695–700.

Swedo SE, Rapoport JL, Cheslow DL, Leonard HL, Ayoub EM, Hosier DM *et al.* (1989*a*) High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. *American Journal of Psychiatry*, **146**, 246–249.

Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A *et al.* (1989*b*) Cerebral glucose metabolism in childhood-onset obsessive-compulsive disorder. *Archives of General Psychiatry*, **46**, 518–523.

Taylor AE, Saint-Cyr JA, Lang AE (1986) Frontal lobe dysfunction in Parkinson's disease: the cortical focus of neostriatal outflow. *Brain*, **109**, 845–883.

Teuber H-L (1964) The riddle of frontal lobe function in man. In: *The Frontal Granular Cortex and Behavior*. Edited by J. M. Warren and K. Akert. New York: McGraw-Hill, pp. 410–444.

Teuber H-L (1966) The frontal lobes and their function: further observations on rodents, carnivores and subhuman primates, and man. *International Journal of Neurology*, **5**, 282–300.

Todes CJ, Lees AJ (1985) The pre-morbid personality of patients with Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **48**, 97–100.

Tucker GJ, Campion EW, Silberfarb PM (1975) Sensorimotor functions and congitive disturbance in psychiatric patients. *American Journal of Psychiatry*, **132**, 17–21.

Tuke DH (1894) Imperative ideas. *Brain*, **17**, 179–197.

Vujić V (1950) Larvate encephalitis and a new extrapyramidal syndrome. *Monatsschrift für Psychiatrie und Neurologie*, **120**, 249–281.

Vujić V (1952) Larvate encephalitis and psychoneurosis. *Journal of Nervous and Mental Disease*, **116**, 1051–1064.

Walker E (1981) Attentional and neuromotor functions of schizophrenics, schizoaffectives, and patients with other affective disorders *Archives of General Psychiatry*, **38**, 1355–1358.

WARD CD (1988) Transient feelings of compulsion caused by hemispheric lesions: three cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, **51**, 266–268.

WECHSLER D (1958) *The Measurement and Appraisal of Adult Intelligence*. Fourth edition. Baltimore: Williams and Wilkins.

WEILBURG JB, MESULAM M-M, WEINTRAUB S, BUONANNO F, JENIKE M, STAKES JW (1989) Focal striatal abnormalities in a patient with obsessive-compulsive disorder. *Archives of Neurology, Chicago*, **46**, 233–235.

WEINBERGER DR, BERMAN KF, ZEC RF (1986) Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia: 1. Regional cerebral blood flow evidence. *Archives of General Psychiatry*, **43**, 114–124.

WEXBERG E (1937) Remarks on the psychopathology of oculogyric crises in epidemic encephalitis. *Journal of Nervous and Mental Diseases*, **85**, 56–69.

WEXBERG E (1938) The organic background of obsessions and compulsions. Discussion. *American Journal of Psychiatry*, **94**, 1415–1416.

WILLIAMS AC, OWEN C, HEATH DA (1988) A compulsive movement disorder with cavitation of caudate nucleus. *Journal of Neurology, Neurosurgery, and Psychiatry*, **51**, 447–448.

WILSON SAK (1927) The tics and allied conditions. *Journal of Neurology and Psychopathology*, **8**, 93–103.

WORLD HEALTH ORGANIZATION (1978) *Mental Disorders: Glossary and Guide to Their Classification in Accordance with the Ninth Revision of the International Classification of Diseases*. Geneva: World Health Organization.

YARYURA-TOBIAS JA, NEZIROGLU FA (1983) Related disorders. In: *Obsessive-Compulsive Disorders*. New York: Marcel Dekker, pp. 105–121.

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APPENDIX

Vignettes of patients showing slowness (*see* text and tables for neurological and neuropsychological findings in each case)

Case A. This 25-yr-old man gave a 10-yr history of a compulsion to touch things and repeat certain actions, which had become associated with marked slowness. For example, a bath might take up to 2 h because of his need to touch and arrange objects in the bathroom, or repeat actions such as turning taps on and off. He was unable to walk forward more than a few paces without reaching to the ground to pick something up that distracted and appeared to 'threaten' him. There was a noticeable difference between his spontaneous, non-automatic behaviour and that of more automatic action, such as that required to catch a ball, or play a game of table tennis at which he was quite skilled. There was no past medical history or family history of relevance At the time of assessment he was not taking any medication. Intensive inpatient behaviour therapy did not lead to any significant improvement.

Case B. This patient was a 27-yr-old woman who gave a 4-yr history of fears of contamination by cobwebs, dust, fur, hairs, fluff, etc., together with a variety of searching rituals and profound slowness in day-to-day activities Cleaning her teeth could take up to 4 h, switching a light on or off up to 30 min, having a bath up to 3 h and eating a meal up to 10 h She would frequently feel compelled to count to a certain number before initiating an action. Her mother suffered from manic-depressive psychosis. There was no other relevant family history. She had no past medical history She was on no medication at the time of assessment Behaviour therapy produced only slight improvement which was not maintained without supervision, and she was felt to be unmotivated to pursue treatment

Case C. This patient was a 49-yr-old woman who gave a 32-yr history of fears of contamination from faeces associated with elaborate washing, checking and avoidance rituals and marked slowness. Her history had pursued a course of fluctuating intensity. At the time of assessment she took up to 10 min to open a door by the handle, up to an hour to use the toilet to defaecate and up to 2 h to have a bath. One of her sisters suffered from depression, but there was no other relevant family history She had no significant past medical history. At the time of assessment she had received no drugs for several months. Intensive behaviour therapy produced a marked improvement in her symptoms including her slowness, and it was possible to discharge her after 2 mths

Case D. The patient was a 37-yr-old man who presented with extreme slowness in most day-to-day activities, e g. washing, opening a door, switching on the television, etc , which he would feel compelled to perform in certain repetitive, ritualistic ways and with frequent checking. His rituals were often associated with fears of germs and contamination, though sometimes he could not explain them. His history started insidiously at the age of 11. There was no family history of psychiatric illness. He was born by breech delivery but no adverse sequelae were reported. A chronic seborrhoeic dermatitis developed at about the same time as his mental difficulties. There was no other past medical history of note At the time of admission and for about 2 yrs he had been taking 20 mg diazepam, 100 mg dothiepin, 100 mg codeine phosphate and paracetamol 6 5 g daily. Behaviour therapy produced a marked improvement, but this was not maintained after discharge.

Case E This male patient was aged 17 yrs and gave an 18 mth history of compulsions to repeat everyday actions involved in, for example, washing, dressing, tying a shoelace, walking through doorways or eating a meal, and to do many similar things in a strict and unchanging order and routine. He described difficulty in making decisions. His parents described that at home he appeared like a slow-motion film There was no relevant family history. At the age of 7 yrs his mother noted that he had a squint and was 'not blinking with his right eye', though at the time he was otherwise well both physically and psychologically. There was no other relevant medical history He had been on no medication for 15 mths before assessment A decision was made to admit him for inpatient behaviour therapy.

Case F. This 46-yr-old man presented with extreme slowness associated with indecision, and a desire to do things perfectly and in the correct order His history of slowness dated from early childhood He had rigid routines for most actions such as dressing, and would become agitated if his routines were disrupted. No other obsessional thinking was evident and no rituals were observed He would take up to 2 h to bath, 1 h to brush his teeth, 5 h to dress, 1 h to eat a meal, or 2 h to use the toilet to pass urine. Neurological examination revealed features consistent with a parkinsonian syndrome of unknown aetiology

One of his brothers suffered from alcoholism but there was no other relevant family history. He was born by forceps delivery after a stressful labour. His milestones were said to have been delayed. There was no other past medical history of significance. At the time of assessment he had received no drugs for several months. Intensive behaviour therapy failed to improve his slowness. He received a trial of L-dopa and a striking objective and subjective improvement was observed during the first 5 d of treatment. However, this improvement was not sustained, though at the patient's request the drug was continued as he described that it made him feel more comfortable

Case G This 18-yr-old man complained of slowness and an inability to make decisions associated with checking rituals, particularly involving electrical appliances, taps, switches and doors To open and close a refrigerator might take half an hour. His ritualistic behaviour started at about the age of 8 and had persisted with fluctuating intensity. There was no family history of neuropsychiatric disorder. A number of drugs had been tried unsuccessfully, but he had received no psychotropic medication for at least 6 mths before examination. An intensive inpatient behavioural programme reduced his symptoms by about 50% but progress was not maintained outside hospital.

Case H. This patient was a 25-yr-old man, with a 10-yr history of odd, repetitive and ritualistic behaviour associated with prominent slowness in day-to-day activities. For example, when tying a shoelace he would be concerned to place the laces at symmetrical angles on either side of the shoe and would repeat components of the tying action. Interruption of his rituals would often lead to aggressive outbursts This patient's obsessive-compulsive behaviour was associated with an abnormal psycho-social development thought to be consistent with the additional diagnosis of Aspberger's syndrome. There was no definite family history of mental or other illness, and no history of cerebral insult Behaviour therapy led to a slight diminution of his ritualistic behaviour, but improvement was not sustained outside hospital.

Case I. This 21-yr-old man had a 12-yr history of obsessional fears concerning self-injury and contamination. He feared injury to his bones if he bumped into things or had to use any physical force, and would consequently move as slowly and as carefully as possible when, for example, walking through doorways or opening doors by the handle. He also feared contamination from any object he touched, and would repeatedly wash his hands. He was markedly slow and could take up to 7 h to brush his teeth, or up to 3 h to have a bath. There was no family psychiatric history He was enuretic until the age of 8 though his development was otherwise unremarkable Behaviour therapy produced worthwhile improvement, but he became reluctant to continue treatment outside hospital and discharged himself after a month.

Case J. This 45-yr-old man had a history of a tic of the head and neck developing at the age of 7 followed some 3 yrs later by compulsions to destroy things of value, to harm himself, to twitch and shout obscenities and to hoard unnecessary objects. Daily activities were constantly interrupted by his compulsions leading to marked slowness in, for example, dressing, bathing or eating a meal. For 10 yrs he complained of a compulsion to echo things that he heard, for example, exclamations on the television, or voices in a crowd or cinema. His father and paternal grandmother had obsessive-compulsive personality traits, and the former also abused alcohol No other relevant family neuropsychiatric history was elicited. A diagnosis of obsessive-compulsive disorder in association with Gilles de la Tourette syndrome was made. An intensive inpatient behavioural programme produced clear improvement in his obsessions and compulsions, but this was not sustained at follow-up.

Case K. This 45-yr-old woman presented with a 4-yr history of a variety of obsessions concerning, for example, asbestos, dirt, chemicals, dentists; AIDS and men exposing themselves to her, associated with lengthy and repetitive washing, cleaning and checking rituals. She complained of slowness in completing everyday actions and would take up to 20 min to cross a road, 4 min to switch a light or a tap off, or half an hour to make a bed. Many of her symptoms had been variably present since the age of 18, sometimes associated with depression She had been taking a course of an MAOI antidepressant until 2 wks before assessment when her drug treatment was discontinued There was no family history of formal neuropsychiatric disorder. A behavioural programme led to clear improvement in her symptoms and slowness such that she was able to return home

Case L. This patient was a 36-yr-old woman who since childhood had carried a diagnosis of Gilles de la Tourette syndrome but who had been admitted to hospital for treatment of severe obsessive-compulsive symptoms and slowness in day-to-day activities increasing over the past 6 yrs Compulsions to ruminate about past conversations and events, lest some disaster befall her, constantly interrupted activities such as washing or dressing, resulting in marked slowness There was no family history of neuropsychiatric disorder and no other past medical history of significance A behavioural programme led to a significant increase in speed and reduction in her obsessional ruminations and checking behaviour such that she was able to return to work Further treatment at home maintained her progress

Case M. This 55-yr-old man presented with a 25-yr history of obsessional doubting and with obsessional fears of electrocution, contamination or injury with sharp objects. He had extensive searching and checking rituals, and he was very slow in his daily life, needing up to 12 h to have a bath, 2 h to comb his hair, 3 h to brush his teeth, 4 h to dress or 15 min to close a window or door For some years he had ceased to resist his obsessions and compulsions which were no longer associated with anxiety. His brother suffered from chronic schizophrenia There was no other family history of neuropsychiatric illness He was offered further inpatient behavioural treatment for his symptoms but he declined as he felt he would be unable to comply with instructions

Case N. This 22-yr-old woman gave a history of ritualistic, repetitive behaviour since the age of 11, which for the past 3 yrs had become associated with obsessions about causing harm or death to befall her family or friends. Her rituals included. 'having to listen for a sound' before starting any action; counting to herself in multiples of 3 whilst doing certain actions, and repetitive washing in a certain order involving a complex series of additional actions such as looking at her rings at various stages She was very slow and would take 2 h to have a bath, 1 h to wash her hands or 10 min to open a door by the handle. She had suffered episodes of depression and of self-harming and disturbed behaviour, and for 12 mths had received flupenthixol decanoate 40 mg fortnightly as part of the management of her self-harming behaviour One of the patient's brothers suffered from petit mal epilepsy but there was no other family history of neuropsychiatric disorder Behaviour therapy initially produced a marked reduction in her symptoms and slowness but this was not sustained outside hospital and she became unable to comply with further treatment.

Case O This 44-yr-old woman had obsessions about dirt and contamination, prolonged hand-washing and cleaning rituals, and marked slowness She described having to pre-plan every movement and to move slowly so as to avoid possible contamination by touching something. Her illness had started at the age of 10 and had pursued a course of fluctuating intensity ever since At about the age of 40 a coarse resting tremor of the left arm together with a slight loss of dexterity in the left hand developed, and an additional diagnosis of idiopathic Parkinson's disease was made. She had taken no medication for many years A maternal aunt had been an inpatient in a psychiatric hospital for an unspecified mental disorder, but there was no other definite family history of psychiatric or other illness The patient's birth and development were normal apart from encopresis until the age of 6 Behaviour therapy produced a significant reduction of her rituals and an acceleration in many day-to-day tasks such that she could return home. She remained on no psychotropic or anti-parkinsonian medication

Case P This 20-yr-old man presented with a 4-yr history of slowness and compulsive checking, touching and repeating rituals, and obsessional ruminations about trivial aspects of past conversations. Meal-times were especially associated with ritualistic behaviour, e.g walking round and round the table before sitting down to eat, or holding his cutlery in a certain manneristic way He would need up to 6 h to have a bath, 4 h to dress, and several hours to eat a meal He had a sister with mental handicap of unknown cause, but there was no other relevant family history Details of his birth and development were unavailable although he was said to have had mild unspecified educational difficulties. There was no past medical history of note. He was taking no medication Behaviour therapy led to a clear reduction of his rituals though made no impression on his ruminations. However, improvement was quickly lost after discharge

Case Q. This 65-yr-old woman had a 14-yr history of obsessional fears of acquiring or transmitting cancer through direct or indirect contact with others, associated with compulsive cleaning rituals. She was very slow, and using a door handle, switch or tap might take 10 min because of hesitation. Washing her hair might take 1 h, and brushing her teeth 15 min. She avoided touching anything as much as possible. She was not taking any medication at the time of assessment There was no family history of neuropsychiatric illness. She was born 1 mth prematurely and was said to have suffered from cyanotic attacks as a neonate, though her early development was reported as otherwise unremarkable. At the age of 47 she fell and dislocated a cervical vertebra producing a cord-compression which left her with a right cervical root lesion and mild pyramidal weakness in the right arm and leg There was no other relevant past medical history. She was taking no psychotropic medication Behaviour therapy led to a marked improvement in her slowness and obsessive-compulsive symptoms and this was maintained at follow-up several months after discharge.

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DISTURBANCE OF MOVEMENT VISION AFTER BILATERAL POSTERIOR BRAIN DAMAGE

FURTHER EVIDENCE AND FOLLOW UP OBSERVATIONS

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SUMMARY

In 1983 we reported in this Journal a patient who suffered a disturbance of movement vision in a relatively pure form. This uncommon cerebral visual deficit resulted as a consequence of bilateral brain damage affecting the lateral temporo-occipital cortex and the underlying white matter In this paper we present further evidence for the selectivity of the movement vision deficit. Furthermore, follow-up examination did not reveal any significant change which indicates that the disorder appears irreversible. Magnetic Resonance Imaging (MRI) shows bilateral lesions involving the upper (cranial) part of the occipital gyri and the adjacent portion of the middle temporal gyri, with the main focus of damage in the upper (cranial) banks of the anterior occipital sulcus. In addition, cortico-cortical fibre pathways interconnecting occipital, temporal and parietal 'visual' areas are also affected bilaterally. The selectivity of the movement vision deficit and the irreversibility of the disorder strongly support the idea that movement vision is a separate function which is subserved by a visual pathway specialized for the processing of visual motion.

INTRODUCTION

In 1983 we reported on a patient who suffered severe disturbance of movement vision as a consequence of bilateral brain damage involving the lateral temporo-occipital cortex and the underlying white matter (Zihl *et al.*, 1983). The patient had completely lost movement vision in depth, and could only discriminate between a stationary and a moving target in the periphery of her otherwise intact visual fields. In the central visual field some movement vision was spared for horizontally and vertically travelling targets, provided that target velocity did not exceed 10 deg/s. She possessed neither visual movement after-effects nor apparent (phi) visual movement. Visually guided eye and finger movements were also impaired. In contrast, her movement perception elicited by acoustic and tactile stimuli was not impaired. We have argued that the selectivity and specificity of the reported visual disorder support the idea that movement vision represents a separate and genuine visual function which depends on neuronal mechanisms beyond the primary visual cortex. This assumption is meanwhile supported by a number of studies in primates. Dubner and Zeki (1971) and Zeki (1974) were the first to report that neurons in the cortex of the posterior bank of the superior temporal sulcus [V5 complex, Zeki and Shipp (1988)] are selective for the direction and velocity of motion of visual stimuli. There is good evidence now that there exists a 'motion area' which

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is involved in the processing of speed and direction of visual stimuli (*see* Maunsell and Newsome, 1987, for a review).

Recently, other brain-damaged cases with selective loss of certain aspects of motion perception have been reported (Vaina, 1989). Single case studies can sometimes be of particular value in neuropsychological research (Shallice, 1988) because some deficits can be observed only in a very small number of patients. On the other hand, they contain the difficulty of deriving generalized conclusions and hence are of limited value if the evidence put forward is not sufficiently convincing. In our case, the evidence for the *selectivity* of the movement vision disorder as put forward in our first report was incomplete because it was limited mainly to elementary visual functions. In this paper we report further observations expecially on the patient's visual object and space perception abilities. Furthermore, we report follow-up data which underline the irreversibility of the disorder. Despite some successful adaptation to her visual disability, the patient's deficit itself has not undergone significant change since our last report, i.e. 10 yrs after the occurrence of brain damage, and 6 yrs and 9 mths after the first detailed experimental investigation of her movement vision disturbance. We have repeated some of the experiments on our patient's movement vision reported in our earlier paper. A detailed analysis of her movement vision using forced-choice discrimination psychophysics has been published elsewhere (Hess *et al.*, 1989; Baker *et al.*, 1991). These investigations have revealed significant threshold elevations for the direction and velocity perception.

One critical issue regarding the *specificity* of the movement vision disorder in our patient has been addressed in a recent paper (Hess *et al.*, 1989). We could demonstrate that the disorder cannot be explained by impaired spatial and/or temporal contrast sensitivities. One of the most crucial factors has been ruled out by this evidence, namely a selective reduction of sensitivity of the more peripheral (up to and including striate cortex) temporal and spatial 'filters' as the possible cause for her disturbed movement vision. This is consistent with some of our earlier findings, namely that her 'temporal resolving power', as judged by the critical flicker fusion and identification of the temporal order of visual stimuli, was not impaired (Zihl *et al.*, 1983).

CASE REPORT

In this case report only information regarding the present state of the patient is communicated (for her earlier state, *see* Zihl *et al.*, 1983).

The patient, now 53-yrs-old, reported that her problems with moving objects and persons remained essentially unchanged since the first examination in 1980. However, she now shows some adaptation to her disorder in that she tries to ignore visual motion as much as possible and especially avoids situations where many objects are moving simultaneously. In this way she is able to manage her household by herself (she lives alone), to go shopping and to use public transport. She has learned to cope to some extent with more than one person walking at the same time by trying intentionally to fixate on only one person at a time while ignoring all the others. She uses a similar strategy in listening to a speaking person. She looks away from the face of the speaker, concentrating just on listening and thus not being disturbed by the unrest of the speaker's mouth. In contrast, she has never reported any difficulties in perceiving simultaneously several objects or persons when at rest

Despite her efficient coping (verified by two of the authors several times outside the laboratory and the hospital), she cannot, for example, cross a road without traffic lights, because she is still unable to judge the speed of a car. If more cars are approaching, the situation is even more difficult and she gets extremely worried. Furthermore, she totally avoids crowded places and streets because 'the more people walk the more difficult and unpleasant it is'. The above mentioned improvement in coping with the movement vision disorder is, however, not sufficient to allow her to work.

The increased fatiguability reported earlier continues, as does the general slowing of all mental processes. The mild anomic aphasia which equally involves all modalities also persists.

MRI analysis

MRI was performed in April 1989, i.e. 1 month after the experiments described in this report were finished. Eight coronal MR-images were obtained with a Magnetom 1,0 T; TE 25 − 90 (slice thickness 4 mm). The anatomical description of the patient's brain lesions is based on the CNS-atlas of Nieuwenhuys *et al.* (1988). The T_2-weighted image through the splenium of the corpus callosum shows small spots of high signal intensity in the middle level of the optic radiation on the right side (and possibly also on the left side). On a T_1-weighted image through the widened posterior horns of the lateral ventricles and the central cerebellar nuclei, the middle temporal gyrus and the adjacent portion of the occipital gyri seem to be severely damaged on both sides. A large zone of high signal intensity involves also the tapetum, the optic radiation (stratum sagittale) and the lateral occipital and occipito-parietal white matter on both sides (T_2-weighted image). In addition, an extended infarction (with haemosiderin deposits) is present in the posterior lobe of the right cerebellar hemisphere.

Fig. 1A shows a coronal section through the deepest parts of the calcarine sulcus. The T_1-weighted image shows that the medial temporal gyrus, the upper (cranial) portion of the occipital gyri, a minor portion of the inferior parietal lobule and the lateral occipito-parietal white matter are damaged on the right side.

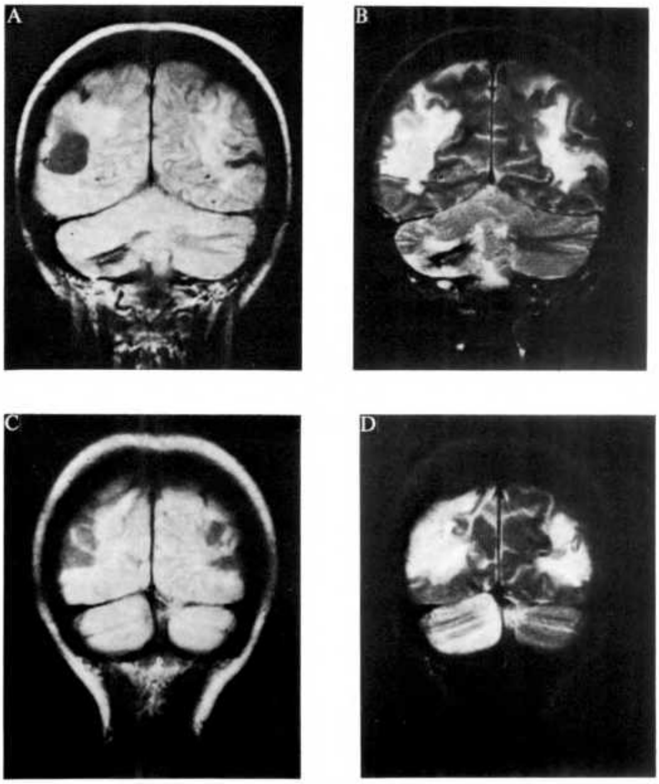

FIG. 1. Four coronal MR images. A − D, for description, *see* text.

On the left side the lesion only comprises the banks of the anterior occipital sulcus injuring adjacent parts of the middle temporal and the occipital gyri. The inferior parietal lobule seems to be spared.

On the T_2-weighted image (Fig. 1B) high signal intensity zones are visible which involve the occipital and the occipito-parietal white matter in both hemispheres. On the right side the changes are much more extensive than on the left side.

Fig. 1C shows a coronal section through the posterior parts of the calcarine sulcus. In the T_1-weighted image there is a bilateral homologous lesion of the upper portion of the occipital gyri sparing its lower (caudal) parts. The medial border of the lesions ends on both sides about 2–3 cm lateral to the midline. The T_2-weighted image demonstrates that the high signal intensity zones reach further medially to the region of the lunate sulcus (Fig. 1D).

The aetiology of brain damage in our patient was reported earlier (Zihl *et al.*, 1983). The outcome of the MRI indeed corroborates our assumption that the bilateral lesions (necrosis and gliotic reactions) might have been caused by a venous thrombosis in the territory of the occipital branches of the superior (and possibly the inferior) cerebral veins. The initial presumably haemorrhagic lesion in the right posterior lobe of the cerebellum might also be the consequence of a venous thrombosis rather than the result of an ischaemic infarction.

METHODS AND RESULTS

The experiments and tests were performed over a period of 6 wks in February/March 1989 with the patient's consent. If not indicated otherwise, all measures were taken under binocular viewing conditions with natural pupils. All luminance values were obtained by means of an electronic photometer (Spectra Spotmeter, Model 1510D-UB 1°). Room illumination was measured using an electronic lux and illuminance meter (Gossen Panlux electronic 2).

For statistical analysis of data we used conventional *t* tests, taking a single trial in a series of measurements as the unit of analysis. One-tailed tests were used to test differences between the patient and a matched normal control subject, and two-tailed tests for all comparisons of conditions within a single subject. Because the conditions (e.g. velocity or position of a stimulus) were assigned to trials in a random order, effects of serial dependencies between adjacent measurements were minimized. Given the randomization of conditions conventional *t* tests are appropriate even for analysis of single case data (Kazdin, 1982).

Since the patient found the inspection of moving stimuli in general very unpleasant and disturbing and, in addition, tired easily, breaks of 2–3 min were introduced after about 10–15 min of testing. The patient was always fully informed about the testing conditions. Instructions were always repeated before restarting the examination. A normal subject (female, 46-yrs-old) served as a control in most of the experiments. Neither subject was ever informed about the outcome of testing during or after single experiments. If not indicated otherwise, methods were identical with those used in the earlier paper (Zihl *et al.*, 1983).

Visual capabilities other than movement vision

The visual fields, critical flicker fusion and detection performance under double simultaneous stimulation conditions (DSS) which were tested under the same conditions as in the earlier report were essentially unchanged when compared with the outcome in the earlier examination. The patient's relative acuity values for Snellen letters were 0.90 for far and 1.00 for near vision (corrected) in either eye. Corrected near monocular reading acuity was Nieden 1. Binocular vision and simultaneous foveal vision were within normal limits, as were fusion, accommodation and convergence. Stereopsis as tested with Titmus and TNO tests was normal; stereoacuity was about 170 sec of arc (range of 5 measurements was 120–240 sec of arc). Discrimination of greys was tested using the grey chips available in the 'New Colour Test de Lanthony Selon Munsell' from Luneau Ophthalmologie, Paris (Lanthony, 1974). For testing of colour discrimination the FM-100 hue test was used (Farnsworth, 1943). Both tests were carried out binocularly under daylight conditions. Sorting of greys (9 chips) was errorless. Colour sorting in the FM-100 hue test is within normal limits (total error score = 206).

In summary, foveal visual performance corresponds mostly to that reported in the earlier paper. Sorting of greys had not been tested in the earlier examination; colour discrimination is now slightly improved (total error score in Zihl *et al.*, 1983: 250).

Visual space perception. In our first report we tested localization performance only for various positions along the horizontal axis by means of saccadic eye movements. Since the patient's saccadic localization performance was perfect, we did not retest her but investigated various other visual spatial abilities.

Distance perception. This was tested along the horizontal axis in both hemifields, and in depth. A perimeter arc was used to test distance estimation along the horizontal axes (Zihl and von Cramon, 1986). Diodes mounted at eye level along the arc served as targets. Their size was 15 min of arc, their luminance 2.4 cd/m^2. The distance between the diodes was 2.5 deg visual angle. To prevent the patient using visual spatial cues, background luminance was set at 0.06 cd/m^2. She was seated at a distance of 100 cm from the perimeter arc, her head was fixed by a head and chin rest. In the centre of the arc a green diode was mounted which also served as fixation point. Two red diodes were simultaneously presented, one in either hemifield. The patient was instructed to keep fixation on the green diode and to match the two red diodes with respect to their distance from the green one in the centre in terms of 'equally distant' or not. Fixation was monitored by EOG.

Localization in depth was tested in a similar way except that the green diode was not used as a reference. Diodes were mounted at a distance of 1 cm along two metal bars reaching from 50 to 130 cm from patient's eyes. They appeared at an angle of 10 deg below eye level. Both bars passed in parallel straight ahead at a distance of 1.5 cm from each other. The patient was instructed to keep the head fixed but was allowed to move her eyes in order to match the distances of two simultaneously flashed targets. Again she was asked to respond with 'equally distant' or 'not equally distant'.

Presentation time was always 3.2 s; interstimulus interval varied between 3 and 8 s. Order of presentation, i.e. selection of each pair of diodes to be matched for distance, presentation time and interstimulus intervals were controlled electronically.

Fig. 2 shows the patient's distance matching along the horizontal axes (A) and in depth (B). Under all testing conditions she performed entirely normally, not exhibiting over- or under-estimation or large variability of estimations as shown by brain-damaged patients with impaired distance perception (Zihl and von Cramon, 1986).

Subjective vertical and horizontal axes. Patients with occipito-parietal damage sometimes shift their subjective vertical and/or horizontal axes away from the corresponding objective axes (Bender and Jung, 1948). We tested our patient's subjective vertical and horizontal axes by asking her to adjust a bar so that it appeared subjectively vertical or horizontal. A yellow bar (18 × 1 deg) was presented on a dark background

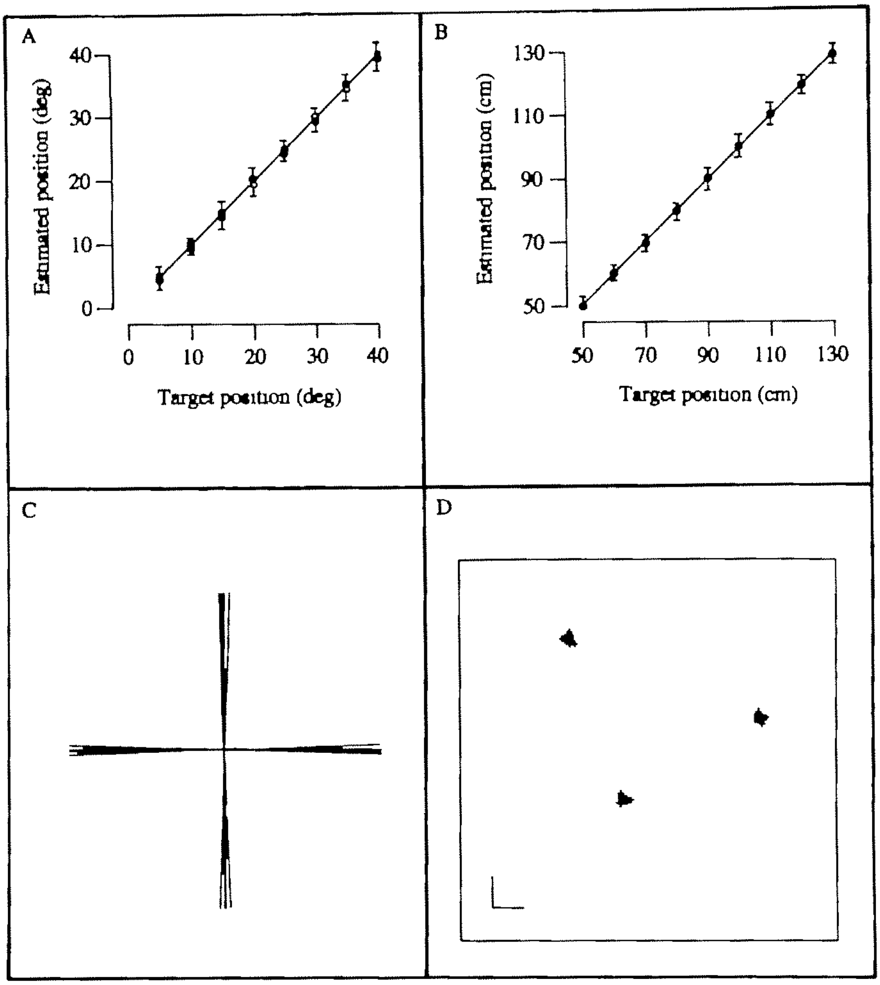

FIG. 2. Results of testing visual spatial abilities. A, estimation of horizontal distances in the left (open circles) and right hemifield (filled circles) B, in depth (cyclopean eye condition) Abscissa positions of targets, ordinate. patient's mean estimated positions. Vertical bars indicate ±1 SD (n = 10 measurements per position). C, adjustment of subjective vertical and horizontal axes (the thin lines indicate the range of 10 measurements per condition). D, position matching (n = 5 trials per position). Black squares indicate standard positions, crosses indicate patient's matching. For further details, *see* text

on a high resolution screen (size 25×19 deg) at a distance of 60 cm. The luminance of the bar was 2.2 cd/m^2, and luminance ratio (stimulus to background) was 11:1. Room illumination was about 5 lux. The bar was rotated either clockwise or anticlockwise in steps of 1 deg between 105 and 75 deg (vertical axis) or between 345 and 15 deg (horizontal axis). The patient was instructed to indicate in each run whether the bar was vertical (horizontal) or not. Because of the low background and room luminances the outline of the screen was invisible and could not be used as a reference. A

PC-system was used for presentation of the bar and for collecting and analysing the data. Presentation time was not limited. Fig. 2c shows patient's mean subjective vertical and horizontal axes and the corresponding ranges. All values were within ±1 deg which is within the range of adjustments of the normal subject.

Line bisection. This was also carried out using a PC-system. A horizontal (18×1 deg) or vertical yellow line (15×1 deg) was presented without time limit. Ten trials were carried out for both axes. The patient bisected both the horizontal and the vertical lines very accurately. Mean horizontal line bisection was at 9.2 deg (range 8.6−9.5 deg), mean vertical bisection was at 7.7 deg (range 7.4−8.2 deg). This result again is in the range of normal performance.

Line orientation. This was tested using the line orientation test (Benton *et al.*, 1975). Each of the orientations was tested three times. Out of 33 measurements the patient only failed in 3. In all cases she chose the line next to the correct orientation. Her line orientation matching performance is well within normal limits published by Benton *et al.* (1978*a*).

Position matching. This was carried out using a PC-system. Three small squares differing in colour (size 0.5 deg) were presented at different positions within a quadratic frame (size 10.4 deg) indicated by thin white lines. A second set of three squares identical in size and colours was presented in one line within a second quadratic frame of the same size. The two frames were, however, vertically displaced by 37 mm, the frame with the squares to be matched being always underneath. The luminance of the squares was the same as for the bars in the test for the subjective vertical and horizontal axes (*see above*). Viewing distance was 60 cm. The patient was instructed to match the position of the three squares individually. Fig. 2D shows that patient's position matching performance is entirely normal.

Object and face perception. The following object- and face-perception abilities were tested: (*a*) matching of object and facial properties, (*b*) object constancy, (*c*) recognition of unfamiliar faces involving face constancy. Responses were recorded in terms of correct, false positive and false negative responses. In addition, the time required to perform the individual tests was recorded.

Matching of object and facial properties. This was examined using tests described in Zihl and Wohlfarth-Englert (1986). The tests consist of matching of parts of objects or faces with the complete object or face, and were found to be sensitive for object vision impairments after occipito-temporal damage.

Object constancy. This was tested using different perspective views of familiar objects. In accordance with other reports (e.g. Warrington, 1982), patients with occipito-temporal brain damage find this kind of object matching difficult (Zihl and Wohlfarth-Englert, 1986).

Facial recognition and face constancy. These were tested by means of the facial recognition test (Benton *et al.*, 1978*b*). This test includes matching of identical front-view photographs of a face (Part A), matching of a front view with views from different angles (Part B), and matching of front-view photographs under different lighting conditions (Part C).

Table 1 shows the data of the patient in the various object and face perception tests, including the performance of a larger group of normal subjects (partly taken from the study by Zihl and Wohlfarth-Englert, 1986). The results show that patient's performance

TABLE 1. PERFORMANCE (ERRORS) AND MEAN TESTING TIME IN THE OBJECT- AND FACE-PERCEPTION TESTS

	Errors		*Time (min)*	
Type of task	*N*	*P*	*N*	*P*
Matching part-whole objects (6)	00	00	1.4 (0.4–1.8)	2.1
Matching part-whole faces (6)	00	00	1.6 (0.5–1.9)	2.3
Object constancy				
('unfamiliar views'; 6)	00	00	0.5 (0.3–0.85)	1.1
Face recognition Test A (6)	00	00	2.8 (1.2–3.2)	4.1
Face Recognition Test B (4)	03	01	3.2 (1.8–4.7)	6.2

Number of test items is given in brackets. N = Normals (n = 30); P = Patient.

lies well within the range of normal performance, except that she again showed marked slowness.

In summary, the patient performed entirely normally in various tests involving visual spatial and object vision abilities. Response times were, however, prolonged in all tests, which is in agreement with her own complaints that most things take much longer than they did before the illness, and with the observation of a general slowing of mental processes (*see also* data on reaction times in the next section).

Movement vision

The patient's movement vision was investigated using experimental procedures similar to those reported in the earlier study (Zihl *et al.*, 1983). We tested detection with stationary and moving targets (horizontal and vertical directions) and with targets moving in depth. In addition, displacement detection thresholds, motion prediction, and movement after-effects and apparent (phi) movement were examined. As it is known that knowledge of the particular stimulus movement condition improves movement detection in normals (Sekuler and Ball, 1977), the particular conditions were always shown in detail to the patient before carrying out an experiment, and at least 10 warm-up runs were given for any condition.

If not indicated otherwise, target luminance was between 3.5 and 5 cd/m^2, and luminance of the always structureless background field was 0.32 cd/m^2. The distance between the screen and the patient was 64 cm. The testing room was darkened (illumination: about 4 lux) to prevent the subjects using visual cues for detection, discrimination or matching of visual movement. Viewing conditions were always binocular with natural pupils.

Motion detection. The testing of detection of targets moving horizontally or vertically was carried out under conditions very similar to those used in the earlier investigation. Briefly, a circular spot of light (size: 1 deg visual angle) was shown moving on a high resolution screen. The length of the path was either 20 deg (horizontally) or 16 deg (vertically). The speed of the target was varied between 1 and 30 deg/s. The patient was instructed to press a response key as soon as she could detect the target moving. She was allowed to fixate the travelling spot (efferent motion perception, Brandt *et al.*, 1973), because we have found in the earlier study that under this condition her residual movement vision was better. The time between the onset of motion and patient's response was defined as movement detection time. In addition, we recorded her response time to the onset of a stationary target. The normal subject was tested in the same way in all conditions. All time measurements were taken by means of an electronic counter (Tektronix DC 503), whereby the counter was triggered by the onset of the target and stopped by the response of the subject.

Fig. 3 summarizes mean detection times for the various stimulus velocities and directions of movement for the patient and the normal subject. The differences between the two subjects are in all conditions statistically highly significant (smallest $t = 18.25$; df $= 38$, $P < 0.001$). For the normal subject, significant differences were found neither between the two horizontal or vertical movement directions (largest $t = 0.37$, df $= 18$, $P > 0.50$) nor between the various stimulus velocities (largest $t = 0.72$, df $= 18$, $P > 0.20$), except for the lowest stimulus velocity (1 deg/s) for both the horizontal and the vertical directions of movement (smallest $t = 2.47$, df $= 18$, $P < 0.05$). For the patient, direction of movement had also no significant effect on movement detection times for the horizontally moving target (largest $t = 0.21$, df $= 18$, $P > 0.80$). For the vertical direction, only for the two lowest stimulus velocities (1 and 3 deg/s) significantly different detection times were found. The downward moving targets were detected significantly faster (smaller $t = 3.46$, df $= 18$, $P < 0.01$). Regarding stimulus velocities, movement detection times were significantly higher for targets moving slower

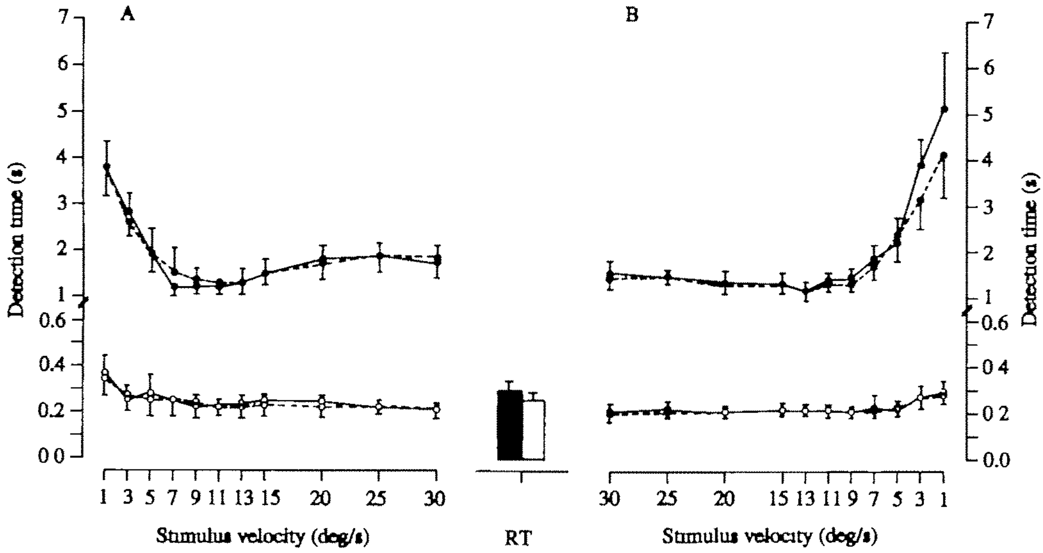

FIG 3. Mean detection times (in s) of the patient (filled circles) and a normal subject (open circles) for a moving target as a function of stimulus velocity and direction of movement. A, horizontal; B, vertical movement direction; continuous lines = target moving from left to right in A, and up-down in B, stippled lines = target moving from right to left in A, and down-up in B; vertical bars indicate ± 1 SD (n = 10 measurements per condition) The two bars in the middle of the figure show reaction times to the appearance of a stationary light target. Patient's visual reaction time is indicated by the black bar, that of a normal subject by the white bar Vertical bars indicate ± 1 SD (n = 20 measurements per condition)

than 7 deg/s for the horizontal and the vertical movement directions (smallest $t = 2.64$, df = 18, $P < 0.02$). Mean detection time of the appearance of a stationary target (simple reaction time) is shown for comparison in the middle of Fig. 3. The patient's response times were significantly lower than her movement detection time, even when the 20 highest RT-values were used for statistical testing (smallest $t = -7.9$, df = 19, $P < 0.001$). The normal subject showed significantly longer response times only for the two lowest stimulus velocities (1 and 3 deg/s) in both movement directions, when the 20 shortest RT values were used for statistical testing (smallest $t = 2.20$, df = 38, $P < 0.05$). Thus the patient showed generally significantly higher response times for movement detection whereas the normal subject did so only for slowly moving targets. However, it should be noted that the patient's visual reaction times were significantly higher than those of the normal subject ($t = 4.19$, df = 38, $P < 0.001$). The same holds true for acoustic reaction times (stimuli: tones with 600 Hz presented at 60 dB HL). Mean acoustic RT (20 measurements) was 0.242 s for the patient (SD = 0.46) and 0.182 s for the normal subject (SD = 19.5) ($t = 19.83$, df = 38, $P < 0.001$).

Table 2 shows the patient's responses as to the direction of the stimulus movement and her reports about the difficulty of movement detection in the various stimulus velocity conditions. In all conditions she could indicate correctly the direction of the moving spot except for very low speeds. But in practically no condition did she find it *easy* to detect the target movement, and never had any clear impression of movement. As in our earlier study, she found it especially difficult to detect targets moving at either lower or higher speeds. Targets moving at higher velocities (i.e. beyond about 10 deg/s) appeared as jumping from one position to the next. This experience was especially pronounced for targets moving upwards, which she describes as, 'First the target is completely at rest. Then it suddenly jumps upwards and downwards', which she described as, 'Single rain drops falling down'.

Motion displacement thresholds. The displacement threshold is defined as the smallest instantaneous target displacement that can be detected. As Legge and Campbell (1981) have demonstrated, displacement detection appears to depend on the motion sense rather than the position sense. If this assumption is correct, our patient should have difficulties also with this task. The stimulus whose horizontal displacement was to be detected was a small, white rectangle subtending either 12×12 or 24×48 min of arc at the viewing distance of 114 cm. The target was presented for at least 5 s at random positions on the face of a high resolution monitor. The minimal step of target displacement was 1.2 sec of arc. Displacement thresholds were measured by means of a forced staircase technique with at least 11 presentations converging around threshold. Target presentations were intermingled with at least six 'catch' trials where the target remained at rest. Concurrent with an acoustical signal the target appeared and the subject was asked to report whether it had moved or not. All responses were followed by the disappearance of the target. For each target velocity, ranging from 0.16 to 10.2 deg/s, five displacement thresholds were determined. Fig. 4 shows that the patient's displacement thresholds were consistently larger than those of the normal subject; the difference is statistically highly significant (smallest $t = 2.04$, df = 8, $P < 0.005$). Patient's threshold values are especially large at velocities lower than 0.6 deg/s indicating a pronounced impairment to detect the displacement of very slowly moving targets.

Since it is known that foveal neurons in areas V1, MT and MST show a preference

TABLE 2 RESPONSES TO MOVING STIMULI

	A		*B*	
Velocity (deg/s)	*H*	*V*	*H*	*V*
01	16	18	20	20
03	19	19	14	20
05	20	20	13	13
07	20	20	00	06
09	20	20	00	02
11	20	20	07	05
13	20	20	11	07
15	19	20	13	07
20	20	20	17	12
25	19	19	20	17
30	19	20	20	20

A = correct responses for the discrimination of moving stimuli, B = number of 'unpleasant' or 'difficult to detect', moving stimuli; H = horizontal moving targets, V = vertical moving targets n = 20 for each condition.

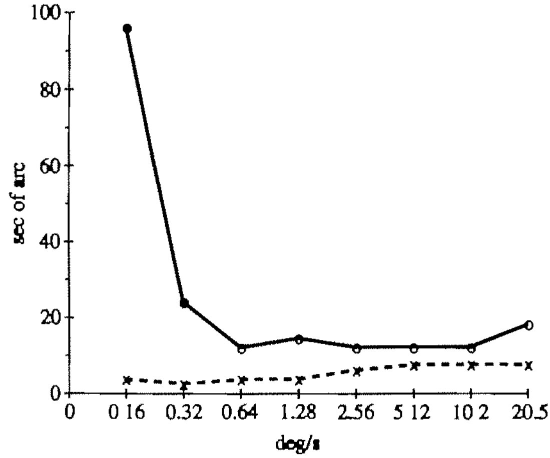

FIG 4. Mean displacement thresholds (in sec of arc) for the patient (full line) and the normal subject (dashed line) as a function of target velocity. For details, *see* text.

for small or large moving objects and low or high stimulus speeds (Orban *et al.*, 1986; Komatsu and Wurtz, 1988*a*,*b*), we also tested movement detection using lower and higher target speeds (2 and 18 deg/s) and smaller and larger targets (bars with a size of either 0.3×0.1 or 1.2×0.8 deg visual angle). Targets were presented on a high resolution screen. All other conditions were the same as described above under the section motion detection. Table 3 shows the results of this experiment. The patient responded significantly faster for the higher stimulus velocities (smaller $t = 3.72$, df $= 18$, $P < 0.002$), but the size of the target had no significant effect (larger $t = 0.78$, df $= 18$, $P > 0.20$). For the normal subject stimulus velocity also showed a statistically significant effect on movement detection but only for the combination of smaller target and lower velocity, in which detection time was highest ($t = 2.28$, df $= 18$, $P < 0.05$). As becomes evident from Table 3, the patient's mean detection times were always higher than those of the normal subject; all differences are statistically highly significant (smallest $t = 15.69$, df $= 18$, $P < 0.001$). A similar picture emerged from the experiment on displacement

TABLE 3. MEAN RESPONSE TIMES TO STIMULI DIFFERING IN SIZE (S) AND MOVING AT DIFFERENT VELOCITIES (V)

		Mean response time (ms)	*SD (n = 10)*
S1/V1	N	313.92	60.2
	P	1363.97	115.2
S1/V2	N	266.38	46.9
	P	1104.55	146.2
S2/V1	N	287.00	46.8
	P	1333.36	205.6
S2/V2	N	254.39	45.7
	P	1042.47	133.8

S1 = 0.3 deg; S2 = 1.2 deg; V1 = 2 deg/s; V2 = 18 deg/s; N = Normal subject; P = Patient.

thresholds. Stimulus size did not significantly affect patient's performance (largest $t = 2.24$, df = 4, $P > 0.05$) except for the two lowest stimulus velocities (0.16 and 0.32 deg/s) (smaller $t = 3.10$, df = 4, $P = 0.04$). In contrast, the normal subject showed significantly lower threshold values in all conditions (smallest $t = 4.00$, df = 4, $P = 0.016$). Taken together, these results show that, in contrast to the normal subject, only stimulus velocity but not stimulus size affected the patient's movement detection.

Detection of movement in the peripheral visual field. This was tested in both hemifields for horizontally moving targets in the same way as in the earlier report. The target was horizontally moved at about 5 deg/s at 30 deg eccentricity in the left or right hemifield. In contrast to the earlier observations, the patient had no difficulty to discriminate between a moving and a stationary target, i.e. did not show any false positive or negative responses. Mean detection times (n = 20 trials) are 1121.5 ms (SD = 239.0) for the left and 1064.2 ms (221.8) for the right hemifield. For comparison, the normal subject required 288.1 ms (35.0) for the left and 271.8 ms (39.6) for the right hemifield. Response times differ significantly in both conditions between the two subjects (smallest $t = 23.26$, df = 22, $P < 0.001$).

Motion in depth. This was tested in a way very similar to that reported in our earlier paper. A black metal cube (size 10 mm) was steadily moved by hand on a table in line of sight either towards the patient or from her. She was seated in front of the table. The path of movement was 100 cm (i.e. viewing distance varied between 30 and 130 cm). Velocities were about 3 and 10 deg/s. Even after intensive practice and testing (20 trials in each condition) the patient never reported any target movement. At 3 deg/s she reported the cube 'jumping back and forth'. At 10 deg/s she found the 'jumping' very uncomfortable. Thus, motion in depth was as impaired as it was in the earlier examination.

Motion prediction. In this experiment the patient was asked to judge the velocity of a light spot moving horizontally in front of her from left to right on a high resolution screen (Tektronix 613). Stimulus conditions were the same as in the experiment on movement detection, except that the target disappeared behind an opaque black mask after it travelled a path of 12 deg. At 20 deg a red marker (18 deg visual angle in height, 1 deg in width) was mounted on the screen indicating the end of the path. The patient was instructed that the target would move horizontally over the screen, and would disappear behind the mask. She should press the response key when the target, now invisible, had reached the red marker. The time elapsed between the onset of target motion to the instant was defined as the total motion time, and served as a measure for motion prediction (Carlson, 1962). Subjects were allowed to fixate the moving target, and to move their gaze towards the red marker corresponding to the invisibly 'moving' target. Before starting the measurements, both subjects were given between 20 and 30 warm-up runs.

Fig. 5 shows the results in motion prediction for both subjects. For the three lower velocities (3 − 7 deg/s) the patient's judgements did not significantly differ from the corresponding values of the normal subject (largest $t = 1.10$, df = 38, $P > 0.20$). For all other stimulus velocities the patient considerably underestimated the speed of the target, and her subjective velocity never exceeded about 10 deg/s. The prediction times differed highly significantly between the two subjects (smallest $t = 3.48$, df = 38, $P < 0.001$). Thus the highest velocity of the horizontally moving target the patient was able to correctly predict was 7 deg/s. This result is practically identical with the corresponding accuracy of prediction in the earlier paper.

Motion after effects. As in the earlier investigation we tested two types of visual movement after-effects. After inspection of the horizontally moving pattern (velocity = 6 deg/s) for 30 s, the patient reported in 4 out of 20 trials that the stripes of the pattern were somehow 'restless', but she never had any impression of movement. The duration of the restless state was very short (between 2.2 and 3.8 s) when compared with the duration of the movement after-effect in the normal subject tested under the same conditions (between 7.4 and 14.9 s; mean = 11.8 s). For testing the spiral after-effect we used a speed of 9 or 18 rpm, corresponding to stimulus velocities of about 6 and 12 deg/s. After an inspection time of 30 s the normal subject reported a clear motion-in-depth after-effect. The patient, in contrast, never reported any effect, not even an 'unrest' of the spiral.

Apparent motion. The patient's ability to perceive apparent visual (phi) motion was tested under the same stimulus conditions as detection of real horizontal motion. Two circular spots of light (size 1 deg visual angle) were each presented for a duration of

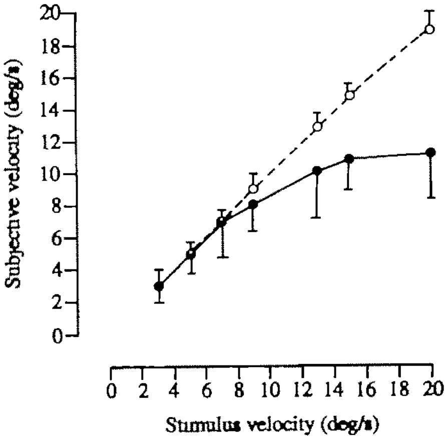

FIG 5. Mean subjective velocity for the patient (filled circles) and a normal subject (open circles) as a function of stimulus velocity calculated from motion prediction experiment. Vertical bars show ±1 SD (n = 20 trials per condition). Stippled line indicates perfect correspondence between stimulus and subjective velocities. For further details, see text.

500 ms. The distance between the spots varied between 1 and 10 deg in steps of 2 deg. Interstimulus intervals varied between 0 and 400 ms. Under no combination of conditions did the patient report apparent movement. She always reported two spots alternatively or simultaneously switched on and off. In contrast, the normal subject reported target movement in conditions known to produce apparent visual motion (Wertheimer, 1912; Korte, 1915).

DISCUSSION

As reported in our earlier paper (Zihl *et al.*, 1983), bilateral posterior brain damage has caused a very unusual and severe disturbance of movement vision in this patient. The disorder is mainly characterized by a difficulty in perceiving moving stimuli in general, whereby all moving objects induce very unpleasant and disturbing experiences, especially when moving at higher velocities. The follow-up examination did not reveal any significant changes, although the patient seems now to cope much better with her visual disability. Despite successful adaptation her movement vision still remained as impaired as it was found to be more than 6 yrs ago.

As pointed out in the Introduction, single case studies are often questionable, but can represent an essential contribution to the understanding of the functional organization of the brain (Shallice, 1988). Therefore, we have tested the patient again and in more detail concerning her visual abilities other than movement vision. Visual fields, detection of stimuli presented simultaneously in the two hemifields, spatial and temporal contrast sensitivities (Hess *et al.*, 1989), acuity, stereopsis, colour and grey discrimination, and various spatial as well as object- and face-perception abilities were found to be entirely in the normal range. Furthermore, in a recent paper (McLeod *et al.*, 1989) we have shown that our patient can perform conjunction search when the target is defined by a conjunction of form and colour, but fails with conjunctions including movement. Thus, the movement vision disorder can be understood as highly specific and selective. The preservation of visual object and space perception indicates that mechanisms in the occipito-temporal and occipito-parietal visual association areas are not substantially affected by the lesion (Cowey, 1982; Desimone and Ungerleider, 1989).

As mentioned earlier, the striate cortex, the occipito-temporal gyri, the lower portion of the occipital gyri, the precuneus and cuneus, the superior parietal lobule, and the angular gyrus are definitely not damaged. Areas that are bilaterally damaged include the upper (cranial) part of the occipital gyri and the adjacent portion of the middle temporal gyri. Regarding these cortical areas, the bilateral and more or less homologous 'lesions' mainly involve the lateral region of visual areas 19, partly extending into adjacent areas 18 and 39. It should be emphasized that the lower halves of the occipital gyri are spared.

As the T1 weighted scans show (Fig. 1) the main focus of the bilateral homologous lesion responsible for the movement vision disturbance in our patient, lies within an area comprising the upper (cranial) banks of the anterior occipital sulcus. The occipital ramifications of the optic radiation(s) are spared. Its more anterior portions (around the lateral ventricle) show high signal intensity, probably as a consequence of reactive gliosis in an incomplete infarction area. As repeated detailed perimetric testing did not reveal any visual field disorder either earlier (Zihl *et al.*, 1983) or in this investigation, these lesions (in the sense of increased signal intensity) obviously are not of any functional relevance. The same holds true for the cerebellar lesion.

The observations on the movement vision disorder in our patient corresponds with the results of physiological experiments in non-human primates which indicate that the middle temporal visual area plays a prominent role in the cortical analysis of visual motion (*see* Maunsell and Newsome, 1987). Furthermore, selective impairments of motion perception (Newsome and Paré, 1988) and of visually guided pursuit eye movements (Newsome *et al.*, 1985; Dürsteler *et al.*, 1987; Dürsteler and Wurtz, 1988) following restricted chemical lesions to area MT support the hypothesis that this visual area in fact contributes essentially to the visual perception of motion. Despite the use of different experimental paradigms, our patient also shows striking threshold elevations for movement detection (*see also* Hess *et al.*, 1989).

Although the chemical lesions in monkeys produced considerable elevations in motion thresholds these deficits showed nearly complete recovery within several days. This is in sharp contrast to the persisting deficit in our patient. However, as found in the earlier report and confirmed by the present observations and, in more detail, in the papers by Hess *et al.* (1989) and Baker *et al.* (1991) the patient is not really 'motion blind' but possesses some kind of movement vision. The evidence presented in the two latter papers also demonstrate that the loss was for judgement of stimulus motion attributes, rather than a reduced sensitivity to moving stimuli as such. As the patient seems to rely exclusively on changes in position of a stimulus and not really on movement itself, one could argue that there is no real residual movement vision capacity at all. On the other hand, as the location and extent of the visual motion area in humans is not known, it might also be understood as the sparing of a small proportion of cells in this area. Alternatively, other visual areas which are also involved in the processing of visual motion, and which are not critically damaged and have access to the striate cortex, could account for the residual movement vision. As no recovery was found over a period of nearly 7 yrs, 'plastic' changes in the damaged brain regions (Newsome and Paré, 1988) can be ruled out. We tried to find further evidence for a preserved function of the damaged motion area, in that we used moving targets which differed in size. Komatsu and Wurtz (1988*a*,*b*) have described differences in receptive field size in MT (foveal region, MTf) and MSTd (anterior bank of STS). Movement detection in the patient was neither influenced by the size of the target nor was an interaction found between target size and stimulus velocity. This might be taken as evidence that neither the homologous foveal nor the dorsal region of MT was functionally spared to a sufficient degree.

If one assumes that the residual movement vision capacity in our patient is subserved by early visual processing mechanisms, i.e. by neurons in areas 17 and/or 18, then one had to expect the inaccurate responses, which were obtained. The number of neurons with direction selectivity subserving central vision is very low (about 10%) in V1 and V2. Furthermore, the majority of cells in V1 and V2 (about 70%) have only a range of optimal speeds with no clear peak in the velocity-response curve. The foveal receptive fields of these V1/V2 neurons are very small (around 0.5 deg). Direction selectivity of these cells depends on stimulus velocity reaching highest direction selectivity at speeds between 2 and 10 deg/s (Orban *et al.*, 1986). These neuronal properties may explain the patient's sensitivity to stimuli moving at stimulus velocities between 5 and 7 deg/s.

The inaccurate responses, e.g. in the displacement threshold and in the velocity prediction experiments, as well as the significantly increased motion detection times, support the hypothesis of early visual processing mechanisms underlying the residual movement vision in our patient (*see also* Baker *et al.*, 1991).

In conclusion, the data and observations presented here are in good agreement with those in monkeys and strongly support the concept of functional heterogeneity of the visual cortex in man which is analogous to that found in non-human primates (Zeki, 1978; Zeki and Shipp, 1988). The demonstration of a highly specific and selective deficit in visual movement perception after bilateral posterior brain damage in our patient suggests that there exists a visual motion area also in the human brain, the exact location and extent of which is not known yet. It seems, however, that cerebral motion blindness can occur as a chronic deficit as has been observed, e.g. for colour blindness (achromatopsia) of central origin (Meadows, 1974, for a review). The 'residual' movement vision capacity, which we still do not understand very well, in the patient's everyday life appears highly disturbing. She complained very often that, 'It would be much easier not to see any restless persons or objects, because it causes such disturbances especially when I am walking'. We could demonstrate that the 'residual' movement vision in our patient does not contribute, e.g. to the active stabilization of posture. On the contrary, we observed a striking active destabilization (Paulus and Zihl, 1989). This indicates that residual functional capacities after brain damage are not always helpful for the patient's adaptation to his disability.

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REFERENCES

Baker CL, Hess RF, Zihl J (1991) Residual motion perception in a 'motion-blind' patient, assessed with limited-lifetime random dot stimuli. *Journal of Neuroscience*, **11**, 454–461.

Bender M, Jung R (1948) Abweichungen der subjektiven optischen Vertikalen und Horizontalen bei Gesunden und Hirnverletzten. *Archiv für Psychiatrie und Nervenkrankheiten*, **181**, 193–212.

Benton A, Hannay HJ, Varney NR (1975) Visual perception of line direction in patients with unilateral brain disease. *Neurology, Minneapolis*, **25**, 907–910.

Benton AL, Varney NR, Hamsher KS de (1978*a*) Visuospatial judgment: a clinical test. *Archives of Neurology, Chicago*, **35**, 364–367.

Benton AL, Hamsher KS de, Varney N, Spreen O (1978*b*) *Facial Recognition. Stimulus and Multiple Choice Pictures*. New York: Oxford University Press.

Brandt T, Dichgans J, Koenig E (1973) Differential effects of central versus peripheral vision on egocentric and exocentric motion perception. *Experimental Brain Research*, **16**, 476–491.

Carlson VR (1962) Adaptation in the perception of visual velocity. *Journal of Experimental Psychology*, **64**, 192–197.

Cowey A (1982) Sensory and non-sensory visual disorders in man and monkey. *Philosophical Transactions of the Royal Society of London, B*, **298,** 3–13.

Desimone R, Ungerleider LG (1989) Neural mechanisms of visual processing in monkeys. In: *Handbook of Neuropsychology*, Volume 2. Edited by F. Boller and J. Grafman. Amsterdam: Elsevier, pp. 267–299.

Dubner R, Zeki SM (1971) Response properties and receptive fields of cells in an anatomically defined region of the superior temporal sulcus in the monkey. *Brain Research, Amsterdam*, **35,** 528–532.

Dürsteler MR, Wurtz RH, Newsome WT (1987) Directional pursuit deficits following lesions of the foveal representation within the superior temporal sulcus of the macaque monkey. *Journal of Neurophysiology*, **57,** 1262–1287.

Dürsteler MR, Wurtz RH (1988) Pursuit and optokinetic deficits following chemical lesions of cortical areas MT and MST. *Journal of Neurophysiology*, **60,** 940–965.

Farnsworth D (1943) The Farnsworth-Munsell 100-hue and dichotomous tests for color vision. *Journal of the Optical Society of America*, **33,** 568–578.

Hess RH, Baker CL, Zihl J (1989) The 'motion-blind' patient: low-level spatial and temporal filters. *Journal of Neuroscience*, **9,** 1628–1640.

Kazdin AE (1982) *Single-Case Research Designs: Methods for Clinical and Applied Settings.* Oxford: Oxford University Press.

Komatsu H, Wurtz RH (1988*a*) Relation of cortical areas MT and MST to pursuit eye movements. I. Localization and visual properties of neurons. *Journal of Neurophysiology*, **60,** 580–603.

Komatsu H, Wurtz RH (1988*b*) Relation of cortical areas MT and MST to pursuit eye movements. III. Interaction with full-field visual stimulation. *Journal of Neurophysiology*, **60,** 621–644.

Korte A (1915) Kinematoskopische Untersuchungen. *Zeitschrift für Psychologie*, **72,** 193–296.

Lanthony Ph (1974) Etude de la saturation au cours des dyschromatopsies acquises au moyen de l'album de Munsell. *Annales d'Oculistique*, **207,** 741–751.

Legge GE, Campbell FW (1981) Displacement detection in human vision. *Vision Research*, **21,** 205–213.

McLeod P, Heywood C, Driver J, Zihl J (1989) Selective deficit of visual search in moving displays after extrastriate damage. *Nature, London*, **339,** 466–467.

Maunsell JHR, Newsome WT (1987) Visual processing in monkey extrastriate cortex. *Annual Review of Neuroscience*, **10,** 363–401.

Meadows JC (1974) Disturbed perception of colours associated with localized cerebral lesions. *Brain*, **97,** 615–632.

Newsome WT, Wurtz RH, Dürsteler MR, Mikami A (1985) Deficits in visual motion processing following ibotenic acid lesions of the middle temporal visual area of the macaque monkey. *Journal of Neuroscience*, **5,** 825–840.

Newsome WT, Paré EB (1988) A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *Journal of Neuroscience*, **8,** 2201–2211.

Nieuwenhuys R, Voogd J, Huijzen C van (1988) *The Human Central Nervous System: A Synopsis and Atlas.* Third Edition. Berlin: Springer.

Orban GA, Kennedy H, Bullier J (1986) Velocity sensitivity and direction selectivity of neurons in areas V1 and V2 of the monkey: influence of eccentricity. *Journal of Neurophysiology*, **56,** 462–480.

Paulus W, Zihl J (1989) Visual stabilization of posture in a case with selective disturbance of movement vision after bilateral brain damage: real and apparent motion cues. *Clinical Vision Sciences*, **4,** 367–371.

Sekuler RW, Ball K (1977) Mental set alters visibility of moving targets. *Science*, **198,** 60–62.

Shallice T (1988) *From Neuropsychology to Mental Structure.* Cambridge: Cambridge University Press.

Vaina LM (1989) Selective impairment of visual motion interpretation following lesions of the right occipito-parietal area in humans. *Biological Cybernetics*, **61,** 347–359.

Warrington EK (1982) Neuropsychological studies of object recognition. *Philosophical Transactions of the Royal Society of London, B*, **298,** 15–33.

Wertheimer M (1912) Experimentelle Studien über das Sehen von Bewegung. *Zeitschrift für Psychologie und Physiologie*, **61,** 161–265.

Zeki SM (1974) Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *Journal of Physiology, London*, **236,** 549–573.

Zeki SM (1978) Functional specialisation in the visual cortex of the rhesus monkey. *Nature, London*, **274,** 423–428.

ZEKI S, SHIPP S (1988) The functional logic of cortical connections. *Nature, London*, **335**, 311–317.

ZIHL J, VON CRAMON D, MAI N (1983) Selective disturbance of movement vision after bilateral brain damage. *Brain*, **106**, 313–340.

ZIHL J, VON CRAMON D (1986) *Zerebrale Sehstörungen.* Stuttgart: Kohlhammer.

ZIHL J, WOHLFARTH-ENGLERT A (1986) The influence of visual field disorders on visual identification tasks. *European Archives of Psychiatry and Neurological Sciences*, **236**, 61–64.

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SUBSTANCE P-CONTAINING NEURONS IN THE MESOPONTINE TEGMENTUM ARE SEVERELY AFFECTED IN PARKINSON'S DISEASE

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SUMMARY

Substance P immunoreactive (SP+) neurons were analysed quantitatively in serial sections of the mesopontine tegmentum in 6 patients with idiopathic Parkinson's disease and 5 age-matched normal controls. In the tegmentum of the Parkinson's disease brains many SP+ neurons contained swollen, twisted neuronal processes as well as Lewy bodies. There were significant reductions in the total number of SP+ neurons in the pedunculopontine tegmental nucleus (loss 43%), in the laterodorsal tegmental nucleus (loss 28%), in the oral pontine reticular nucleus (loss 41%) and in the median raphe nucleus (loss 76%). It was the large SP+ (>20 μm) neurons that were particularly affected. In our control group we did not document a significant relationship between age at death and number of SP+ neurons in these tegmental nuclei or between age at death and number of pigmented neurons in the locus coeruleus. In contrast, in patients with Parkinson's disease, there was a strong inverse relationship between age at death and numbers of SP+ and pigmented neurons. Our findings suggest an interaction between the pathophysiological mechanisms initiated by Parkinson's disease and other processes related to ageing. Since tegmental SP+ neurons are affected by the primary pathological processes underlying Parkinson's disease as severely as catecholamine-synthesizing neurons are affected, theories of pathogenesis and therapeutic strategies in Parkinson's disease will need to take into account the involvement of these SP+ neurons.

INTRODUCTION

The pedunculopontine tegmental nucleus (PPTg) in the mesopontine tegmentum is of particular interest in Parkinson's disease because studies in experimental animals have linked this structure with induction of movement (Garcia-Rill *et al.*, 1987). The large neurons in the human PPTg have been shown to contain choline acetyltransferase (Mesulam *et al.*, 1989) and substance P (Halliday *et al.*, 1990*b*). Studies using Nissl stains and NADPH diaphorase histochemistry have demonstrated Lewy bodies and loss of neurons in this nucleus in Parkinson's disease (Hirsch *et al.*, 1987; Jellinger, 1988; Zweig *et al.*, 1989).

Recently, we analysed the distribution of substance P immunoreactive neurons in the mesopontine tegmentum in 10 human brains from individuals with no apparent neurological disease (Halliday *et al.*, 1990*b*). We counted the immunopositive neurons in coronal sections at 22 rostrocaudal levels in each of 5 brains and mapped their

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distribution in mesopontine areas including the PPTg, the lateral dorsal tegmental nucleus (LDTg), the oral pontine reticular nucleus (PnO) and the median raphe nucleus (MnR). In the present paper we compare the distribution and number of substance P-containing neurons in these nuclei in brains from 6 Parkinson's disease patients and 5 controls. In addition, we have counted the pigmented neurons in the locus coeruleus in both the control and the Parkinson's disease brains to determine whether the disease process affects catecholamine-containing and substance P-containing neurons to a similar extent in different patients. We also examined the relationship between age at death and the number of substance P-containing and catecholamine-containing cells in the various nuclei. We previously reported preliminary data for 3 sections through the PPTg in each of 3 Parkinson's disease brains showing reduced numbers of substance P-containing neurons and Lewy bodies in these cells (Halliday *et al.*, 1990*c*).

MATERIALS AND METHODS

Six brains from patients with clinical histories of idiopathic Parkinson's disease (PD) and 5 age-matched control brains from patients with no apparent neurological diseases were used in this study (*see* Table 1). For 5 of the 6 PD patients the hospital case records contained reliable information concerning the duration of the disease and the extent of the symptomatology. One patient (PD3) was leading a relatively normal life when he died, 5 yrs after the onset of the disease, from acute pneumonia complicating chronic congestive cardiac failure and inactive pulmonary tuberculosis. Four cases (PD6, PD8, PD9, PD11) died at least 20 yrs after the onset of symptoms and the mode of death for these cases appeared to be related to the immobility and inanition which occurs in later stages of the illness. The remaining patient (PD5) died from an acute myocardial infarction after urgent transfer from a nursing home. We were not able to reliably ascertain the duration or stage of her PD.

TABLE 1 DETAILS OF CONTROLS (N) AND PATIENTS WITH PARKINSON'S DISEASE (PD)

Case	*Sex*	*Age at death*	*Post-mortem delay (h)*	*Duration of symptoms (yrs)*
N9	M	64	23	0
N10	F	79	4	0
N13	M	70	11	0
N15	F	59	6	0
N16	F	87	9	0
PD3	M	73	18	5
PD5	F	77	5	?
PD6	M	78	3	23
PD8	M	88	3	20
PD9	F	83	48	30
PD11	M	71	2	24

The brains were removed and fixed within 48 h of death by perfusion of aldehyde through the carotid and vertebral arteries. Details of procedures for removal and fixation of brains have been described previously (Halliday *et al.*, 1990*c*). The brains and sections of the brainstem, hippocampus and cortex were examined by a neuropathologist (P.C.B.), using haematoxylin and eosin, cresyl violet and Bodian-silver stains. The clinical diagnosis of PD was thereby confirmed for each of the 6 PD cases whereas no pathology was found in controls. One brain (PD3) had diffusely scattered senile plaques in the frontal, parietal, calcarine and hippocampal cortices with some neurofibrillary degeneration maximal in the temporal lobe. However, it was not excluded because the histological and immunocytological pathology of the brainstem was predominantly PD. There is very little damage to tegmental nuclei in Alzheimer's disease (Jellinger, 1988; Zweig *et al.*, 1989). There were no significant differences between the control and PD groups with respect to age of the patient at death (72 ± 5 vs 78 ± 3 yrs, respectively, $P > 0.05$) or to post-mortem delay before fixation (10.6 ± 3.3 vs 13.2 ± 7.4 h, respectively, $P > 0.05$). There was no relationship between post-mortem delay and any of the neuronal counts in any of the nuclei for either controls or for PD cases.

Tissue processing and immunohistochemistry

After fixation, brainstems were dissected, measured and carefully blocked in a plane perpendicular to the long axis of the brainstem. Coronal sections (50 μm) were cut on a freezing microtome and collected serially in 15 consecutive containers each containing 1 in every 15 sections. Separate section series were used for routine histological stains and for immunohistochemistry. A monoclonal antibody to substance P (Seralab, Crawley Down, Sussex, UK) was used and the immunoreactivity was visualized using an avidin-biotin-peroxidase and diaminobenzidine system. Selected sections stained for substance P were also counterstained with haematoxylin and eosin to confirm Lewy bodies. A detailed description of our immunohistological procedures has been published previously (Halliday *et al.*, 1990*b*).

Computer-assisted quantitative analysis

The number and position of substance P immunoreactive neurons was recorded using a Macintosh II computer and the Magellan program (Halasz and Martin, 1985). In this system, the microscopic image of the section was reflected via a drawing tube onto the screen of the computer monitor. A cursor cross driven by the computer mouse was superimposed on the screen image, and the length of the cursor cross was defined by justifying the eyepiece and the magnification of the drawing tube. By choosing appropriate software options, morphological details of relevant structures such as outlines of sections and anatomical landmarks, and the size and position of immunoreactive cells were entered in the computer using a cursor to trace or mark the structures. The digitized spatial coordinates produced by the Magellan program were read by a Wingz (Informix Software, Kansas) program to generate computer reconstructions of the sections.

In order to minimize effects of sampling on cell counts, only those cases without loss of any sections between the caudal midbrain and the rostral half of the pons were used. Sections stained for substance P were carefully oriented and outlines of the section and of major reference structures (cerebral aqueduct, central grey, medial longitudinal fasciculus, central tegmental tract, superior cerebellar peduncle, cranial nerves, and well-defined nuclei like the red, oculomotor, trochlear, trigeminal nuclei) were mapped in the computer. The positions and shapes of these stuctures were compared with adjacent haematoxylin and eosin, cresyl violet and Weil stained sections to define the rostrocaudal level. This procedure was also used to match section level between different brains. There were no significant differences between the control and PD groups in the length of the tegmentum, measured as the distance from the caudal pole of the red nucleus to the first section in which the facial nerve appeared (18 ± 0.3 mm for the control, and 17.3 ± 0.4 mm for PD, $P > 0.05$). Nor were there significant changes in the rostrocaudal extensions of the particular nuclei: PPTg, control 6 ± 0 2 mm, PD 6.3 ± 0.3 mm; LDTg, control 8.2 ± 0.4 mm, PD 8.6 ± 0.4 mm; PnO, control 11 ± 0.2 mm, PD 11.3 ± 0.8 mm, MnR, control 10.3 ± 0 4 mm, PD 10.5 ± 0.2 mm ($P > 0.05$ for all comparisons) Therefore it was possible to compare directly equivalent serial sections from control and PD brains. The rostrocaudal extent of the mesopontine nuclei examined meant that 23 or 24 sequential sections (from the original 1 in 15 series) were examined in each control and PD brain.

Cell counting and measurement

Under 250× magnification, SP+ neurons were counted and sorted into 'large' or 'small' cells, according to whether their largest soma axis was greater or less than 20 μm. Pigmented locus coeruleus cells in the same sections were also marked. All counting was executed by 1 investigator (W.P G.). Recounting of randomly selected sections (no less than 5 from each brain) by the same and another investigator (W.W.B.) revealed a high interobserver correlation coefficient ($r = 0.93$).

In the mesopontine tegmentum, major groups of large SP+ neurons were centred in the PPTg, LDTg and PnO nuclei, but were not confined within traditional nuclear boundaries. Positive cells were also dispersed between these cell groups. At some rostrocaudal levels it was difficult to assign particular SP+ neurons to individual nuclei, especially in the case of the LDTg and PnO. For quantitation purposes we therefore found it helpful to use MacSpin (D^2 Software, Inc., Austin) to construct a three-dimensional image of the various SP+ cell distributions, rotated about some readily defined anatomical landmark. Thus the main body of the PPTg SP+ neuron group was located in the caudal midbrain dorsolateral or lateral to the superior cerebellar peduncle, while the PnO SP+ neurons were located medially to the superior cerebellar peduncle, in the rostral pons. In the midbrain and pontine central grey, the LDTg SP+ neurons were demarcated by the dorsal margin of the lateral extension of the medial longitudinal fasciculus. The MnR SP+ group was clearly delineated from these groups. The more caudally located pontine raphe SP+ cells were excluded from counting.

Statistical methods

We first compared ipsilateral and contralateral SP+ cell counts for the various nuclei in each control or PD case. Correlations between cell numbers on both sides of each section from all brains ranged from 0.86 to 0.98 (all significant at $P < 0.01$). Ipsilateral and contralateral numbers of cells in each section were compared for each particular nucleus. No significant differences were found ($P > 0.05$, unpaired Student's t test). Results from both sides were therefore pooled and multiplied by 15 to give a total number of SP+ neurons for each nucleus. Correction factors were not used because the sections were 50 μm thick and the immunohistochemical reaction product obscured the nucleolus.

Comparisons between cell counts for corresponding nuclei in PD and control brains were performed using multiple analysis of variance and Fisher's protected least significant difference test. Pearson product moment correlations between the number of SP+ neurons in the various nuclei and the number of locus coeruleus pigmented cells were calculated. Linear regression and analysis of covariance were used to examine the effects of age on the cell counts in PD and control brains.

RESULTS

Pathological changes in substance P immunoreactive neurons in Parkinson's disease

Immunohistochemistry revealed substantial degenerative changes in SP+ neurons of the pedunculopontine tegmental nucleus (PPTg), laterodorsal tegmental nucleus (LDTg) and the oral pontine reticular nucleus (PnO) in patients with PD. Degenerating SP+ neuronal elements included swollen and twisted axons and dendrites (Figs 1A,D, 2B), swollen terminal boutons, somata with dark-stained nuclei (Fig. 1C), Lewy body-like inclusions (Fig. 1A,B,C). The inclusions, more heavily stained for substance P in their peripheral zones than in their cores, were identical to classical Lewy bodies when counterstained with haematoxylin and eosin. Lewy bodies occurred most often in the somata of larger SP+ cells, especially in the PPTg where they were present in as many as 25% of remaining SP+ neurons in cases PD3 and PD11 (counted in 1 section through the middle level of the PPTg). In the MnR, Lewy body-containing SP+ neurons were rare. These morphological changes were not observed in SP+ neurons in control brains.

Topography of substance P immunoreactive neurons in Parkinson's disease

The topographic distribution of SP+ neurons was examined in coronal sections and in three-dimensionally reconstructed images. In controls (*see also* Halliday *et al.*, 1990*b*), many large and some small SP+ neurons were located in the PPTg, LDTg and PnO nuclei (Figs 2A,C,E), while the MnR contained mainly small SP+ cells (Fig. 3D). In the PPTg, large SP+ neurons were concentrated in the dorsolateral compact part and were dispersed medially, whereas small SP+ neurons occurred mainly ventromedial to the large cell constellation (Fig. 3A); in the LDTg and PnO, large and small SP+ neurons were more evenly mixed (Fig. 2C,E).

In PD brains a substantial loss of SP+ neurons was apparent (Fig. 2B,D,F). The

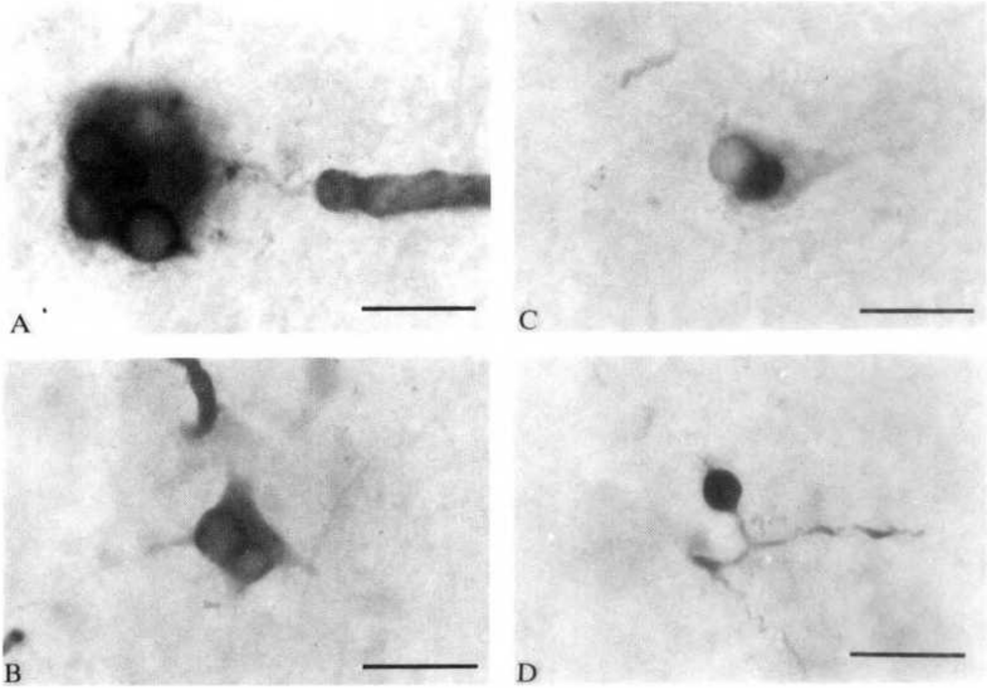

FIG. 1. Photomicrographs showing Lewy body-containing SP+ neurons in PPTg (A), LDTg (B), and PnO (C), and a swollen SP+ neuronal process in the LDTg (D). Bar = 25 μm.

distribution of SP+ neurons was markedly reduced in coronal sections through the PPTg, with large SP+ neurons being principally affected (Figs 2B, 3C, 4). There was also a reduction in SP+ cell densities within the LDTg (Figs 2D, 3F) and the PnO (Figs 2F, 3F).

The three-dimensional reconstructions shown in Fig. 5 present a global view of the tegmental distribution of SP+ neurons as well as pigmented locus coeruleus cells in representative brains from control and PD groups. In the reconstructions there is obvious loss of large SP+ neurons (yellow dots) in the PPTg, LDTg and PnO nuclei. Loss of small SP+ neurons (red dots) is most severe in the MnR, but less obvious in the LDTg nucleus. The concurrent loss of locus coeruleus neurons (blue dots) is also evident.

Quantitation of loss of substance P immunoreactive and pigmented cells in Parkinson's disease

Table 2 gives the total number of SP+ neurons in the mesopontine tegmental nuclei as well as the number of pigmented locus coeruleus cells, for both control and PD groups. In PD brains there was a significant reduction in numbers of SP+ neurons in all the mesopontine tegmental nuclei examined as well as a significant reduction in the number of pigmented cells in the locus coeruleus. Reduction of SP+ cells was most marked in the MnR, comprised mainly of small SP+ neurons, with 76% of SP+ neurons lost. Significant loss of SP+ neurons also occurred in the PPTg (43% loss), the LDTg (28%

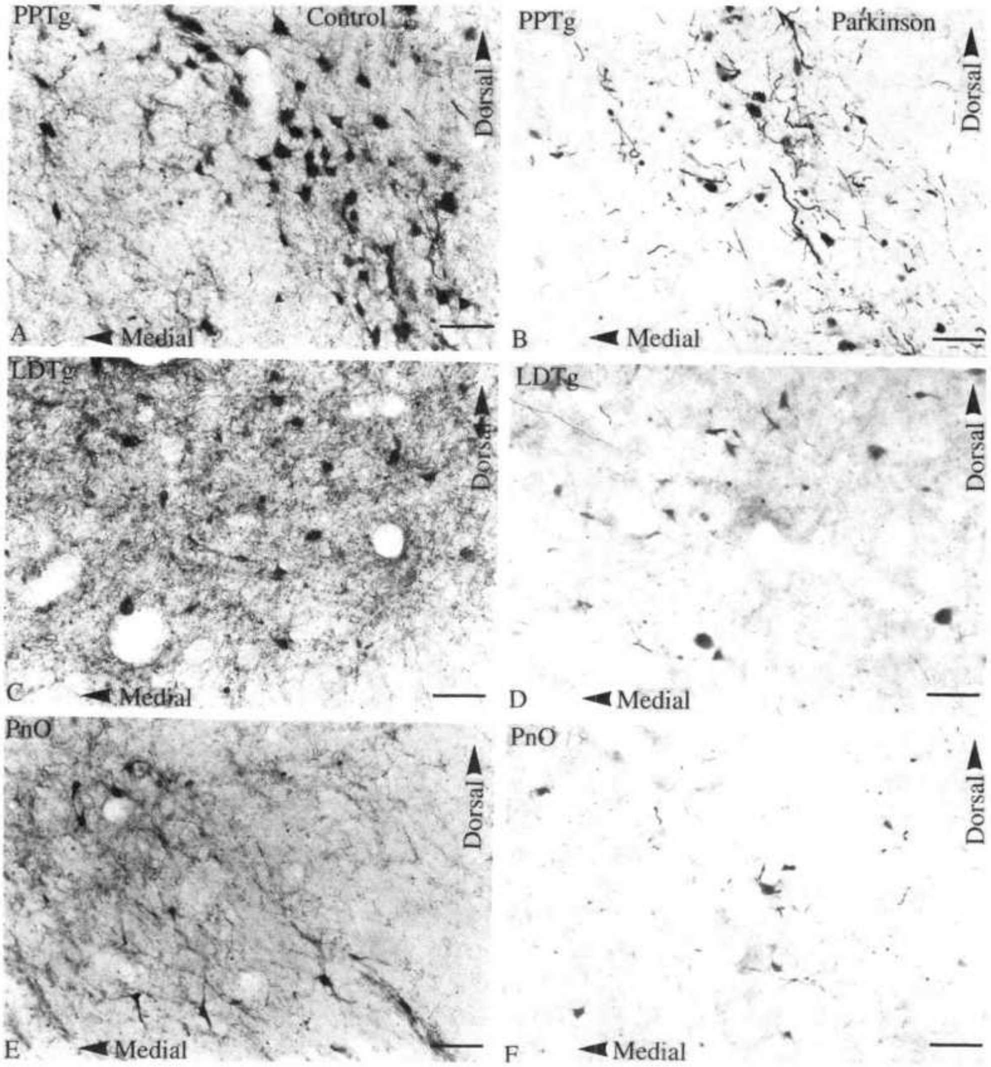

FIG. 2. Photomicrographs of immunohistochemically processed sections showing SP+ neurons in control and PD brains. Bar = 100 μm.

loss) and the PnO (41% loss). In the latter nuclei, loss of large SP+ cells was more severe than loss of the small cells (Table 2).

Relationships between either age at death of duration of symptoms and number of substance P immunoreactive and pigmented cells

In the control group linear regression analysis demonstrated no relationship ($P > 0.05$) between age at death and number of SP+ cells in any of the mesopontine tegmental nuclei (Fig. 6). Similarly there was no significant relationship ($P > 0.05$) between age at death and number of locus coeruleus pigmented cells (Fig. 6). However, in the PD

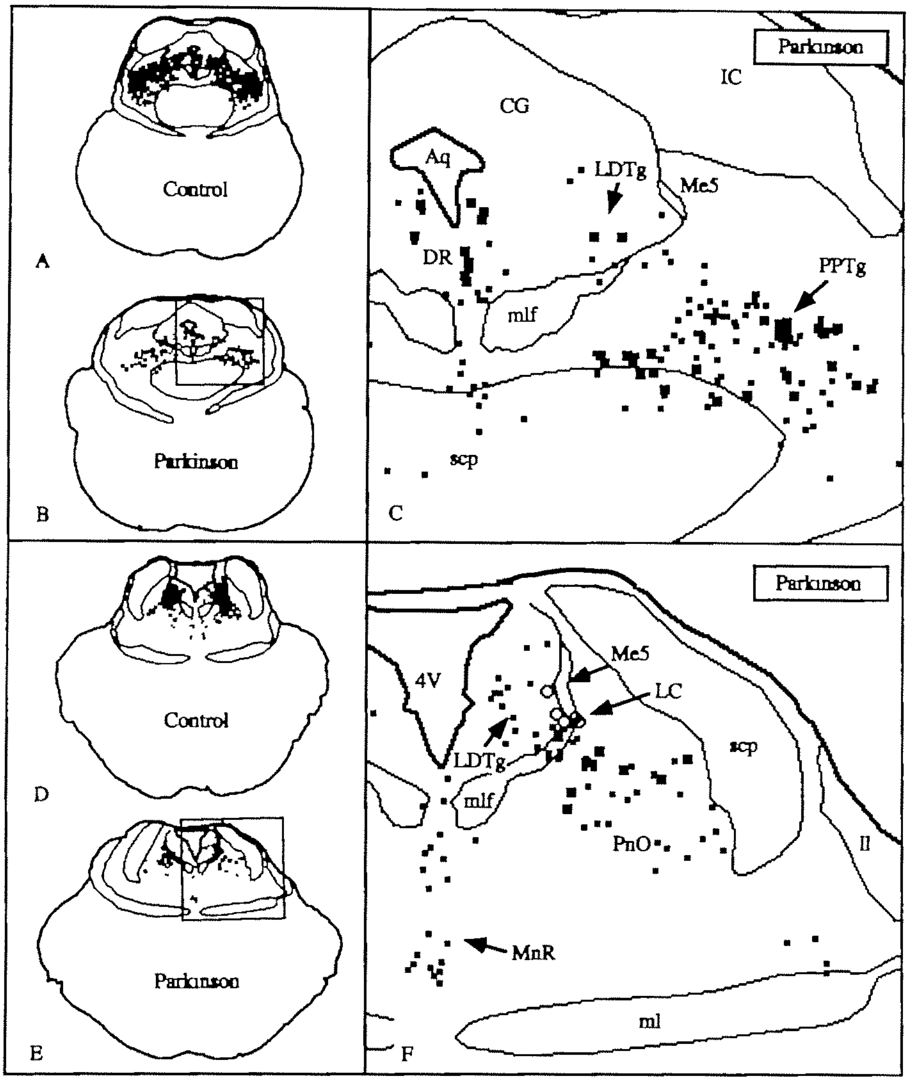

FIG 3 Computer-generated diagrams showing position of large (large filled squares) and small (small filled squares) SP+ neurons and pigmented locus coeruleus cells (open circles) at two rostrocaudal levels from control (A,D) and PD brains (B,E) The indicated regions in (B) and (E) are shown in (C) and (F). Abbreviations: 4V, fourth ventricle; Aq, cerebral aqueduct; CG, central grey; DR, dorsal raphe nucleus IC, inferior colliculus, ll, lateral lemniscus; LC, locus coeruleus, LDTg, laterodorsal tegmental nucleus; Me5, mesencephalic trigeminal nucleus; ml, medial lemniscus; mlf, medial longitudinal fasciculus; MnR, median raphe nuclei; PnO, oral pontine reticular nucleus, PPTg, pedunculopontine tegmental nucleus; scp, superior cerebellar peduncle

group there was a strong relationship between age at death and number of cells in many of the tegmental nuclei (Fig. 6). Patients dying at an older age had fewer total SP+ cells in all of the mesopontine tegmental nuclei except the MnR, and fewer pigmented cells in the locus coeruleus. In the PPTg and the LTDg the most negative correlation

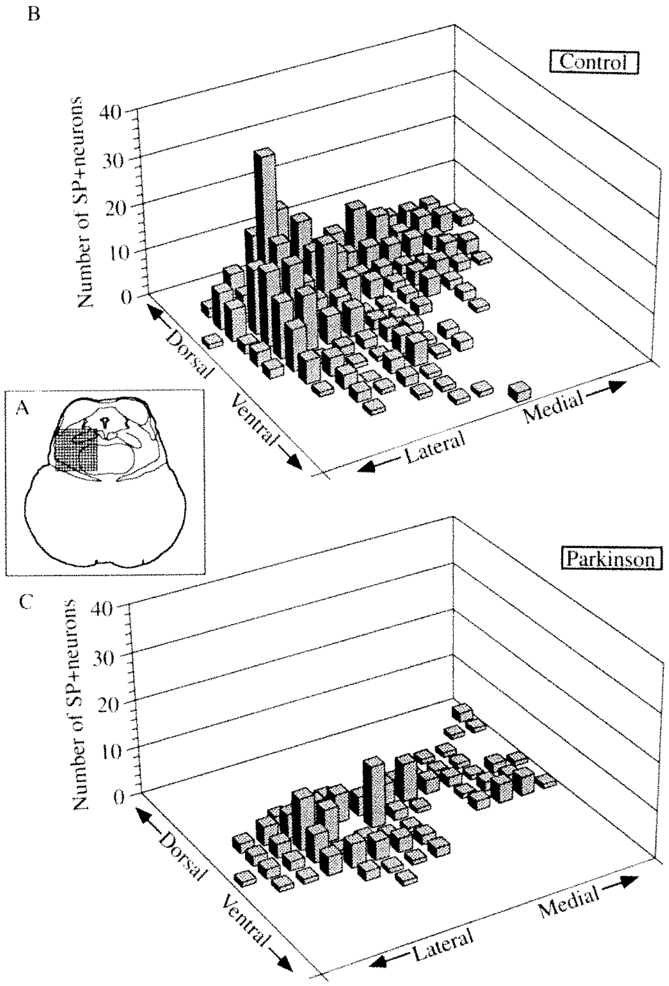

FIG. 4. Histogram showing numbers of SP+ neurons in the region of the PPTg indicated in (A) in a control (B) and a PD brain (C).

was between age at death and the number of large SP+ neurons ($r = 0.91$, $P < 0.05$ for PPTg and $r = 0.92$, $P < 0.01$ for LDTg). In the PnO age at death was negatively correlated with both large and small SP+ cell numbers ($r = 0.82$, $P < 0.05$ and $r = 0.92$, $P < 0.01$, respectively).

We examined the relationship between cell number and duration of symptoms for the 5 PD patients with well-documented records. There was no significant relationship ($P > 0.05$) between duration of symptoms and number of SP+ cells in any nucleus or between duration of symptoms and number of pigmented neurons in the locus coeruleus. Nor was there a significant relationship between age at death and duration of symptoms.

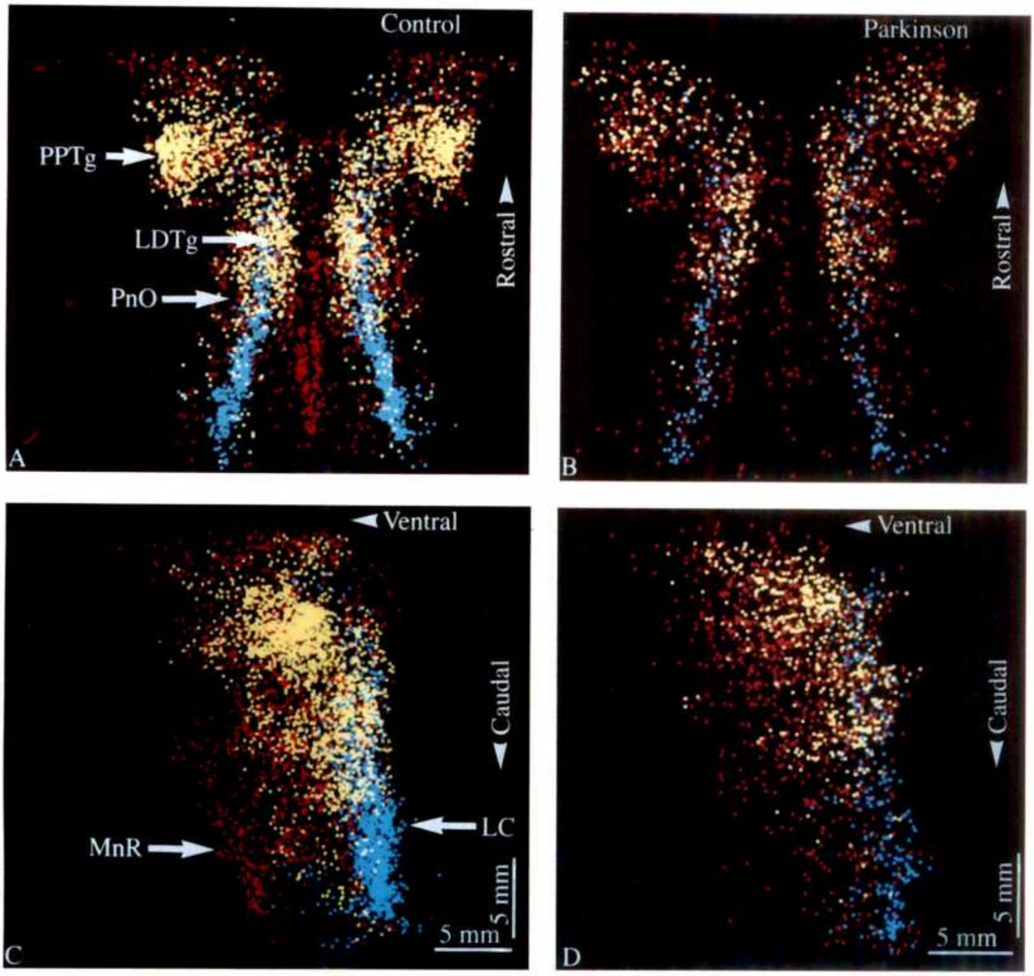

FIG. 5. Three-dimensional reconstructions of distribution of large (yellow dots) and small (red dots) SP+ neurons and pigmented cells in the locus coeruleus (blue dots) in control (A,C) and PD (B,D) brains. A and B are dorsal views, and C and D are lateral views. The number of cells in the reconstruction images was reduced to 1/45th of actual cell numbers.

Relationship between number of substance P immunoreactive cells and number of locus coeruleus cells

In brains from control patients, correlation analysis revealed no relationship between the number of pigmented cells in the locus coeruleus and the number of SP+ cells in any of the mesopontine nuclei we examined. In the PD brains, in contrast, there was a significant correlation between the number of locus coeruleus cells and the number of large SP+ cells in the PPTg ($r = 0.89$, $P < 0.05$) and in the LDTg ($r = 0.83$, $P < 0.05$). This relationship did not hold for the small SP+ cells in these nuclei but there was a significant relationship between the number of locus cells and the number of small SP+ cells in the PnO in PD brains ($r = 0.86$, $P < 0.05$). The relationship

TABLE 2. SUBSTANCE P IMMUNOREACTIVE CELLS IN PPTg, LDTg, AND PnO AND PIGMENTED CELLS IN LC IN CONTROL AND PARKINSON BRAINS (MEAN ± SEM)

	PPTg	*LDTg*	*PnO*	*MnR*	*LC*
Control (n = 5)					
Total SP+ cells	54465 ± 4493	16822 ± 762	34904 ± 3265	6737 ± 605	45840 ± 1206
Large SP+ cells	36935 ± 3994	10750 ± 534	14937 ± 1851		
Small SP+ cells	17530 ± 1132	7105 ± 772	19968 ± 2193		
Parkinson (n = 6)					
Total SP+ cells	31065 ± 5291**	12038 ± 1392**	20647 ± 3866*	1638 ± 178**	11995 ± 2804**
Percentage loss	43	28	41	76	74
Large SP+ cells	17038 ± 4710*	4904 ± 1089**	5890 ± 2281*		
Percentage loss	54	54	61		
Small SP+ cells	13208 ± 1460*	7134 ± 690	13661 ± 2382		
Percentage loss	25	0	32		

* $P < 0.05$, ** $P < 0.01$, analysis of variance (MANOVA), Parkinson vs control.

between numbers of cells in the various nuclei may have reflected the underlying relationship with age at death (*see* Discussion).

DISCUSSION

The present study demonstrates that many SP+ neurons in the mesopontine tegmentum, especially the large cells, were extensively damaged in the brains of patients with idiopathic Parkinson's disease. Neuronal degeneration, with Lewy body formation and substantial loss of SP+ neurons, was observed in the PPTg, LDTg, PnO nuclei in Parkinson's disease. Loss of SP+ neurons in the PPTg nucleus in Parkinson's disease is consistent with recent reports from several laboratories utilizing counts of large Nissl-stained (>20 μm) cells or NADPH positive cells in this nucleus (Hirsch *et al.*, 1987; Jellinger, 1988; Zweig *et al.*, 1989). These authors reported loss of approximately half of PPTg neurons, similar to the loss of large SP+ cells documented for PPTg in the present study (54%).

There are no previous reports of cell loss or neuropathological changes in the LTDg or the PnO in Parkinson's disease. Our results constitute the first evidence that these nuclei are affected in this condition. We demonstrated loss of SP+ cells in these nuclei and documented pathological changes, including the occurrence of Lewy bodies in immunopositive neurons. We have previously reported the loss of serotonin-synthesizing neurons in the MnR nucleus (Halliday *et al.*, 1990*a*,*c*). Most of MnR serotonin-synthesizing neurons are large cells (Baker *et al.*, 1991). In the present study we report that the small SP+ neurons are also lost from this nucleus in Parkinson's disease. This suggests that different neuronal types can be affected in a single nucleus in Parkinson's disease.

In our Parkinson's disease, duration of symptoms was not related to neuronal loss. This might simply reflect the fact that 2 of the 6 patients died from causes unrelated to the disease process. However, even in the patients dying with conditions related to severe immobility, as a manifestation of their Parkinson's disease, the duration of symptoms was not related to neuronal loss. In individual patients there may have been a progressive loss of neurons with increasing duration of disease but, because Parkinson's

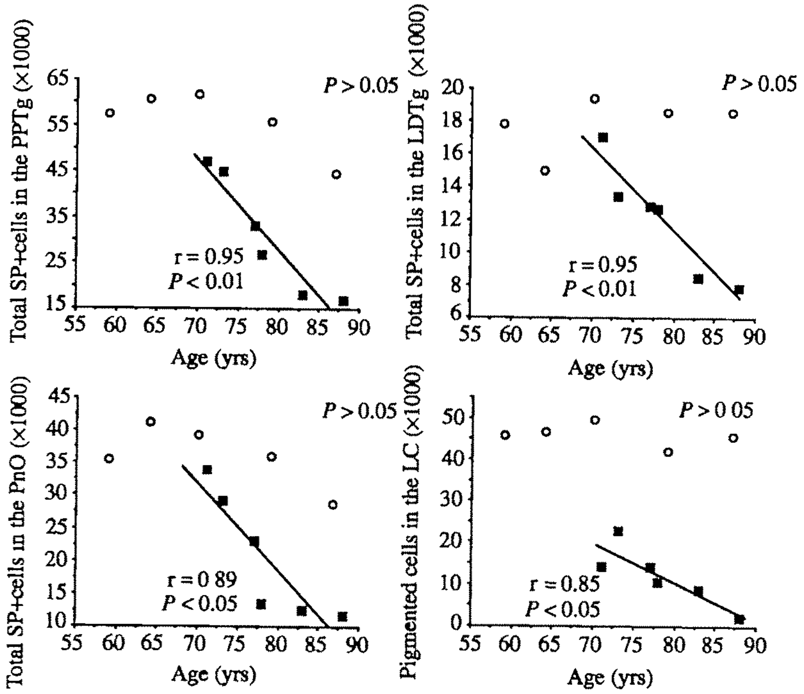

FIG. 6. Age-related changes in the number of SP+ cells in the mesopontine tegmental nuclei and the number of pigmented locus coeruleus cells in control (○) and PD brains (■)

disease progresses at markedly different rates in different patients, our method of analysis did not demonstrate more severe loss of neurons in patients who died after experiencing the symptoms of Parkinson's disease for many years.

In our control brains we did not demonstrate a significant relationship between age at death and the number of cells, either in the locus coeruleus or in the mesopontine SP+ nuclei. This result might reflect our relatively small sample size and the impossibility of obtaining serial counts in an individual patient. However, the results of other investigators who have studied whether or not the number of locus coeruleus neurons decreases with age, clearly demonstrate that there is no consensus regarding this question (Vijayashankar and Brody, 1979; Tomlinson *et al.*, 1981; Iversen *et al.*, 1983; German *et al.*, 1988; Chan-Palay and Asan, 1989). On the other hand, in our Parkinson cases we found a major relationship both between age at death and number of SP+ cells in the various mesopontine nuclei and between age at death and number of pigmented cells in the locus coeruleus. The effects of ageing on neuronal survival are therefore variable, depending on whether or not there is coexistent Parkinson's disease. This interaction between the Parkinson pathophysiological process and the effects of ageing implies that both processes affect a common neuronal site or mechanism, present in both SP+ neurons and in pigmented locus coeruleus cells.

The relationships between age at death and cell number (Fig. 6) indicate that the youngest Parkinson patient had an approximately normal number of total SP+ cells in all nuclei except the MnR (where the regression was not significant). In contrast, all Parkinson patients had depleted numbers of cells in the locus coeruleus, regardless of age at death. This might suggest a more important initial role for catecholamine cell loss in the symptoms of Parkinson's disease, reflecting the excellent response to dopamine replacement therapy experienced by many patients in the early stages of the disease. However, it was notable that Lewy bodies were present in many of the surviving SP+ neurons in our Parkinson case that died after a relatively short duration of disease (PD3). This suggests that SP+ neurons were affected early in the disease and they might have functioned abnormally even if they were present in normal numbers. It is therefore premature to speculate as to which particular neuronal class is more or less relevant to Parkinson symptomatology.

The question arises as to whether the degenerative effects observed in tegmental SP+ neurons are primary, or secondary to degeneration of other neurons. Since the pattern of degeneration in SP+ cells appears no different to that in catecholamine neurons (e.g. both contain Lewy bodies), and there is no evidence for significant cell loss in areas which have major connections with the affected nuclei, it is likely that the effects observed are primary.

The distribution of SP+ neurons in the PPTg, the PnO and the LDTg correspond to the Ch5 and Ch6 groups of acetylcholine-synthesizing neurons described by Mesulam *et al.* (1989). Coexistence of SP and acetylcholine in the tegmental neurons has been demonstrated in animals (Vincent *et al.*, 1983; Standaert *et al.*, 1986) and may also occur in humans (Halliday *et al.*, 1990*b*). Our observations, together with those of Mesulam *et al.* (1989), Hirsch *et al.* (1987), Jellinger (1988) and Zweig *et al.* (1989), imply a loss of acetycholine-synthesizing SP+ neurons in the PPTg, PnO and LDTg in Parkinson's disease.

The anatomical connections and the possible functional role of neurons in the various mesopontine tegmental nuclei are still fairly poorly defined, especially in the human brain. In experimental animals, the PPTg and the LDTg have extensive rostral connections with subcortical structures including thalamus, lateral hypothalamus, lateral preoptic area, substantia innominata, septal nuclei, zona incerta, and ventral tegmental area (Sakanaka *et al.*, 1981; Hallanger *et al.*, 1987; Grove, 1988; Hallanger and Wainer, 1988; Vertes, 1988; Jones and Cuello, 1989; Cornwall *et al.*, 1990). Many of these in turn project to the hippocampus and the cerebral cortex. In humans, a substance P-containing projecting system from the tegmentum to thalamic nuclei has been suggested by Hirai and Jones (1989). Neurons in the PPTg and LDTg have been implicated in complex brain functions such as sleep (Baxter, 1969; Baghdoyan *et al.*, 1984; Gnadt and Pegram, 1986), arousal (Macadar *et al.*, 1974), and memory (Goldberg *et al.*, 1981; Kessler *et al.*, 1986). Impairment in these functions has been observed in patients with Parkinson's disease.

Studies in experimental animals have placed the PPTg, LDTg and PnO in a pivotal position linking forebrain and hindbrain motor control. Many connections of the PPTg, LDTg and PnO neurons are with nuclei associated with movement regulation. The PPTg and LDTg receive afferent inputs from the basal ganglia, subthalamus, nucleus accumbens, substantia nigra (Nauta and Mehler, 1966; Kim *et al.*, 1976; Nauta and Cole, 1978; Beckstead and Frankfurter, 1982; Saper and Loewy, 1982; Edley and

Graybiel, 1983; Jackson and Crossman, 1983; Tokuno *et al.*, 1988). Neurons in the PPTg, LDTg and PnO project to medullary reticulospinal neurons or directly to the spinal cord (Garcia-Rill and Skinner, 1987*b*; Goldsmith and van der Kooy, 1988; Rye *et al.*, 1988; Woolf and Butcher, 1989; Cornwall *et al.*, 1990; Nakamura *et al.*, 1990). Physiological studies have provided evidence that stimulation of PPTg or the medullary area to which it projects, induces locomotion (Garcia-Rill *et al.*, 1987; Garcia-Rill and Skinner, 1987*a*). Substance P may be one of the important neurotransmitters in this pathway (Garcia-Rill *et al.*, 1990; Kinjo *et al.*, 1990).

Our finding that SP+ cells are lost in Parkinson's disease has implications for theories concerning the pathophysiological process underlying the disease. Both catecholamine and non-catecholamine neurons are affected by this process, indicating that neurotransmitters may not be the most important factors rendering the cell vulnerable. Our results also present difficulties for the hypothesis that it is the presence of the neuromelanin which renders cells vulnerable to the Parkinson process, as proposed by Hirsch *et al.* (1988). It will be interesting to see whether MPTP-induced parkinsonism causes loss of mesopontine SP+ neurons.

Current therapies for Parkinson's disease aim at replacing dopamine in the affected pathways, either by pharmacological supplementation or by transplanting dopamine-producing cells into the brain. The impressive loss of non-catecholamine mesopontine neurons documented in the present study and in those of Hirsch *et al.* (1987), Jellinger (1988) and Zweig *et al.* (1989), suggests that attention should also be directed towards replacement of the substance P- and acetylcholine-mediated functions of the various mesopontine tegmental nuclei that are affected in Parkinson's disease.

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REFERENCES

BAGHDOYAN HA, RODRIGO-ANGULO ML, MCCARLEY RW, HOBSON JA (1984) Site-specific enhancement and suppression of desynchronized sleep signs following cholinergic stimulation of three brainstem regions. *Brain Research, Amsterdam*, **306**, 39–52.

BAKER KG, HALLIDAY GM, HALASZ P, HORNUNG J-P, GEFFEN LB, COTTON RGH *et al.* (1991) Cytoarchitecture of serotonin-synthesizing neurons in the pontine tegmentum of the human brain. *Synapse*. In press.

BAXTER BL (1969) Induction of both emotional behavior and a novel form of REM sleep by chemical stimulation applied to cat mesencephalon. *Experimental Neurology*, **23**, 220–229.

BECKSTEAD RM, FRANKFURTER A (1982) The distribution and some morphological features of substantia nigra neurons that project to the thalamus, superior colliculus and pedunculopontine nucleus in the monkey. *Neuroscience*, **7**, 2377–2388

CHAN-PALAY V, ASAN E (1989) Quantitation of catecholamine neurons in the locus coeruleus in human brains of normal young and older adults and in depression. *Journal of Comparative Neurology*, **287**, 357–372.

CORNWALL J, COOPER JD, PHILLIPSON OT (1990) Afferent and efferent connections of the laterodorsal tegmental nucleus in the rat. *Brain Research Bulletin*, **25**, 271–284.

EDLEY SM, GRAYBIEL AM (1983) The afferent and efferent connections of the feline nucleus tegmenti pedunculopontinus, pars compacta. *Journal of Comparative Neurology*, **217**, 187–215.

GARCIA-RILL E, HOUSER CR, SKINNER RD, SMITH W, WOODWARD DJ (1987) Locomotion-inducing sites in the vicinity of the pedunculopontine nucleus. *Brain Research Bulletin*, **18**, 731–738.

GARCIA-RILL E, SKINNER RD (1987*a*) The mesencephalic locomotor region. I. Activation of a medullary projection site. *Brain Research, Amsterdam*, **411**, 1–12.

GARCIA-RILL E, SKINNER RD (1987*b*) The mesencephalic locomotor region. II. Projections to reticulospinal neurons. *Brain Research, Amsterdam*, **411**, 13–20.

GARCIA-RILL E, KINJO N, ATSUTA Y, ISHIKAWA Y, WEBBER M, SKINNER RD (1990) Posterior midbrain-induced locomotion. *Brain Research Bulletin*, **24**, 499–508.

GERMAN DC, WALKER BS, MANAYE K, SMITH WK, WOODWARD DJ, NORTH AJ (1988) The human locus coeruleus: computer reconstruction of cellular distribution. *Journal of Neuroscience*, **8**, 1776–1788.

GNADT JW, PEGRAM GV (1986) Cholinergic brainstem mechanisms of REM sleep in the rat. *Brain Research, Amsterdam*, **384**, 29–41.

GOLDBERG E, ANTIN SP, BILDER RM, GERSTMAN LJ, HUGHES JEO, MATTIS S (1981) Retrograde amnesia: possible role of mesencephalic reticular activation in long-term memory. *Science*, **213**, 1392–1394.

GOLDSMITH M, VAN DER KOOY D (1988) Separate non-cholinergic descending projections and cholinergic ascending projections from the nucleus tegmenti pedunculopontinus. *Brain Research, Amsterdam*, **445**, 386–391.

GROVE EA (1988) Neural associations of the substantia innominata in the rat. afferent connections. *Journal of Comparative Neurology*, **277**, 315–346.

HALASZ P, MARTIN P (1985) Magellan program for quantitative analysis of historical sections. Sydney: University of New South Wales

HALLANGER AE, LEVEY AI, LEE HJ, RYE DB, WAINER BH (1987) The origins of cholinergic and other subcortical afferents to the thalamus in the rat. *Journal of Comparative Neurology*, **262**, 105–124.

HALLANGER AE, WAINER BH (1988) Ascending projections from the pedunculopontine tegmental nucleus and adjacent mesopontine tegmentum in the rat. *Journal of Comparative Neurology*, **274**, 483–515.

HALLIDAY GM, BLUMBERGS PC, COTTON RGH, BLESSING WW, GEFFEN LB (1990*a*) Loss of brainstem serotonin- and substance P-containing neurons in Parkinson's disease. *Brain Research, Amsterdam*, **510**, 104–107.

HALLIDAY GM, GAI WP, BLESSING WW, GEFFEN LB (1990*b*) Substance P containing neurons in the pontomesencephalic tegmentum of the human brain. *Neuroscience*, **39**, 81–96.

HALLIDAY GM, LI YW, BLUMBERGS PC, JOH TH, COTTON RGH, HOWE PRC *et al.* (1990*c*) Neuropathology of immunohistochemically identified brainstem neurons in Parkinson's disease. *Annals of Neurology*, **27**, 373–385.

HIRAI T, JONES EG (1989) Distribution of tachykinin- and enkephalin-immunoreactive fibres in the human thalamus. *Brain Research: Brain Research Reviews*, **14**, 35–52.

HIRSCH EC, GRAYBIEL AM, DUYCKAERTS C, JAVOY-AGID F (1987) Neuronal loss in the pedunculopontine tegmental nucleus in Parkinson disease and in progressive supranuclear palsy *Proceedings of the National Academy of Sciences of the USA*, **84**, 5976–5980.

HIRSCH E, GRAYBIEL AM, AGID YA (1988) Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature, London*, **334**, 345–348.

IVERSEN LL, ROSSOR MN, REYNOLDS, GP, HILLS R, ROTH M, MOUNTJOY CQ *et al.* (1983) Loss of pigmented dopamine-β-hydroxylase positive cells from locus coeruleus in senile dementia of Alzheimer's type. *Neuroscience Letters*, **39**, 95–100.

JACKSON A, CROSSMAN AR (1983) Nucleus tegmenti pedunculopontinus: efferent connections with special reference to the basal ganglia, studied in the rat by anterograde and retrograde transport of horseradish peroxidase. *Neuroscience*, **10**, 725–765.

JELLINGER K (1988) The pedunculopontine nucleus in Parkinson's disease, progressive supranuclear palsy and Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **51**, 540–543.

JONES BE, CUÉLLO AC (1989) Afferents to the basal forebrain cholinergic cell area from pontomesencephalic-catecholamine, serotonin, and acetylcholine- neurons. *Neuroscience*, **31**, 37–61.

KESSLER J, MARKOWITSCH HJ, SIGG G (1986) Memory related role of the posterior cholinergic system. *International Journal of Neuroscience*, **30**, 101–119.

Kim R, Nakano K, Jayaraman A, Carpenter MB (1976) Projections of the globus pallidus and adjacent structures: an autoradiographic study in the monkey. *Journal of Comparative Neurology*, **169**, 263–289.

Kinjo N, Atsuta Y, Webber M, Kyle R, Skinner RD, Garcia-Rill E (1990) Medioventral medulla-induced locomotion *Brain Research Bulletin*, **24**, 509–516.

Macadar AW, Chalupa LM, Lindsley DB (1974) Differentiation of brain stem loci which affect hippocampal and neocortical electrical activity. *Experimental Neurology*, **43**, 499–514.

Mesulam M-M, Geula C, Bothwell MA, Hersh LB (1989) Human reticular formation: cholinergic neurons of the pedunculopontine and laterodorsal tegmental nuclei and some cytochemical comparisons to forebrain cholinergic neurons. *Journal of Comparative Neurology*, **283**, 611–633.

Nakamura Y, Kudo M, Tokuno H (1990) Monosynaptic projection from the pedunculopontine tegmental nuclear region to the reticulospinal neurons of the medulla oblongata. An electron microscope study in the cat. *Brain Research, Amsterdam*, **523**, 353–356.

Nauta WJH, Mehler WR (1966) Projections of the lentiform nucleus in the monkey. *Brain Research, Amsterdam*, **1**, 3–42.

Nauta HJW, Cole M (1978) Efferent projections of the subthalamic nucleus: an autoradiographic study in monkey and cat. *Journal of Comparative Neurology*, **180**, 1–16.

Rye DB, Lee HJ, Saper CB, Wainer BH (1988) Medullary and spinal efferents of the pedunculopontine tegmental nucleus and adjacent mesopontine tegmentum in the rat. *Journal of Comparative Neurology*, **269**, 315–341.

Sakanaka M, Shiosaka S, Takatsuki K, Inagaki S, Takagi H, Senba E *et al.* (1981) Evidence of the existence of a substance P-containing pathway from the nucleus laterodorsalis tegmenti (Castaldi) to the lateral septal area of the rat. *Brain Research, Amsterdam*, **230**, 351–355.

Saper CB, Loewy AD (1982) Projections of the pedunculopontine tegmental nucleus in the rat: evidence for additional extrapyramidal circuitry *Brain Research, Amsterdam*, **252**, 367–372.

Standaert DG, Saper CB, Rye DB, Wainer BH (1986) Colocalization of atriopeptin-like immunoreactivity with choline acetyltransferase- and substance P-like immunoreactivity in the pedunculopontine and laterodorsal tegmental nuclei in the rat. *Brain Research, Amsterdam*, **382**, 163–168.

Tokuno H, Moriizumi T, Kudo M, Nakamura Y (1988) A morphological evidence for monosynaptic projections from the nucleus tegmenti pedunculopontinus pars compacta (TPC) to nigrostriatal projection neurons. *Neuroscience Letters*, **85**, 1–4.

Tomlinson BE, Irving D, Blessed G (1981) Cell loss in the locus coeruleus in senile dementia of Alzheimer type. *Journal of the Neurological Sciences*, **49**, 419–428.

Vertes RP (1988) Brainstem afferents to the basal forebrain in the rat *Neuroscience*, **24**, 907–935.

Vijayashankar N, Brody H (1979) A quantitative study of the pigmented neurons in the nuclei locus coeruleus and subcoeruleus in man as related to aging *Journal of Neuropathology and Experimental Neurology*, **38**, 490–497.

Vincent SR, Satoh K, Armstrong DM, Fibiger HC (1983) Substance P in the ascending cholinergic reticular system. *Nature, London*, **306**, 688–691.

Woolf NJ, Butcher LL (1989) Cholinergic systems in the rat brain: IV. Descending projections of the pontomesencaphalic tegmentum. *Brain Research Bulletin*, **23**, 519–540.

Zweig RM, Jankel WR, Hedreen JC, Mayeux R, Price DL (1989) The pedunculopontine nucleus in Parkinson's disease. *Annals of Neurology*, **26**, 41–46.

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FACTORS AFFECTING VISUAL SENSITIVITY IN A HEMIANOPIC SUBJECT

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SUMMARY

A well-studied subject with visual cortex damage (G.Y.) was tested in his hemianopic field with temporally modulated sinusoidal and square-wave gratings. The purpose was to use an extended range of parameters to obtain a detailed spatiotemporal specification of his residual vision and to try to resolve the discrepancy between negative findings of Hess and Pointer (1989) and previous positive claims. Both the spatial and temporal parameters could be Gaussian-weighted. Detection as a function of spatial frequency, contrast, temporal modulation frequency, stimulus size, and slope of the temporal and spatial Gaussian functions was investigated using a two-alternative forced-choice procedure. The most important parameters for this subject were found to be the slope of the temporal Gaussian function and the size and contrast of gratings. With optimum parameters he could reliably achieve a score of 95–100% correct in his 'blind' field. The results are consistent with earlier studies of this subject, especially his ability to respond to moving stimuli, and also may account for why negative results had been reported for him when particular fixed parameters were used.

INTRODUCTION

A variety of reports have appeared over the past 15 yrs of evidence for residual function in the perimetrically and clinically 'blind' fields of some subjects with field defects caused by damage to the visual cortex (*cf* review by Weiskrantz, 1990). It is becoming clear that the fine details, not only of the probable retino-fugal pathways that may or may not be preserved in such patients, but also of the stimulus parameters that are used to test residual function can be crucial in defining the psychophysical profiles in such cases.

As residual vision is generally best elicited with rapidly presented or fast moving targets, very few studies varied systematically both spatial and temporal factors for retinally localized stimuli within the same stimulus domain. Recently, Hess and Pointer (1989) extended a useful psychophysical approach to 'blindsight' by imposing Gaussian-weighted boundaries on both the spatial and temporal dimensions of their stimuli. The effect of this is to make the stimulus onset and offset, and the spatial edges, gradual rather than abrupt and to do this in a way that can be described precisely and varied systematically and smoothly. It allows one to control and to specify the influence of spatial edge transients and temporal on-off transients.

These authors studied 3 hemianopic subjects but reported, after exhaustive testing, that they could find no residual function in the blind fields using temporally modulated, retinally localized stimuli that lacked spatial structure. Structured stimuli were used in the sighted half-fields only and under these conditions reduced contrast sensitivity for temporally modulated gratings was found.

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The results for the blind fields were surprising, because one of their 3 subjects was G.Y., who has been tested by a number of different investigators who have consistently reported striking residual function in his hemianopic field (Barbur *et al.*, 1980, 1988; Blythe *et al.*, 1986, 1987). These reports stand in contrast to the strong conclusion by Hess and Pointer (1989): '*using experimental conditions which would be expected to reveal even the most restricted and rudimentary spatiotemporal visual capacity, we can report no evidence for residual visual function in any region of the perimetrically blind hemifield of our hemianopic patients*'.

In the present study we used an extended range of parameters to try to obtain a more detailed spatiotemporal specification of G.Y.'s residual vision in order to understand and hopefully to resolve the discrepancy between Hess and Pointer's findings and other positive claims.

The 'blindsight' literature indicates that stimulus size is an important variable (Weiskrantz *et al.*, 1974; Barbur *et al.*, 1980), whereas Hess and Pointer (1989) used what was effectively a small stimulus. Also, G.Y.'s good sensitivity for detecting fast moving targets (Barbur *et al.*, 1980) is of particular interest and relevance in considering the design of optimal stimulus parameters. Accordingly, in the present study we varied the size, the slope of the Gaussian temporal functions, the spatial structure and the properties which determine the temporal contrast modulation of the stimuli in ways that seemed appropriate to G.Y.'s previously reported residual capacities.

METHODS

Apparatus

The stimuli were generated on a high resolution 36 cm square colour monitor (Model HP D1187A) driven by a 60 Hz, non-interlaced graphics card (Model A1083A) The card supports a maximum resolution of 1280×1024 pixels with 256 simultaneous colours selectable from a palette of 16.7 million. Measurement of chromaticity coordinates and the gun voltage luminance relationship for the red, green and blue phosphors were measured using a gamma scientific telespectroradiometer (Model DR-2) and an LMT 1000 luminance meter, respectively. These data were stored in a display calibration file and used by the experimental programs to generate the required visual stimuli (e.g. true, Gaussian-weighted, sinusoidal or square-wave modulation of luminance).

The subject was seated in front of the display, his head movements restrained by an adjustable chin rest and head support. The display was viewed through a large dichroic mirror which has a high, uniform transmittance over the visual spectrum and reflects well in the infra-red part of the spectrum. This arrangement provides an unrestricted field of view and makes possible the continual monitoring of eye-movements. (Details of the operation of the P-SCAN 100 system used in this investigation can be found in Barbur *et al.*, 1987.) The subject's pupils were imaged at high magnification using infra-red light and displayed continuously. The experimenters ensured that steady fixation was established before each stimulus presentation. The subject's responses were recorded automatically and the results tabulated and stored at the end of each experimental session

Stimuli

All stimuli were retinally localized (and eye position continuously monitored). Stimuli were weighted with Gaussian functions in both the spatial and temporal domains. Spatially the weighting was symmetrical with respect to the centre of the stimulus. Similarly, the temporal weighting was symmetrical for both the onset and the offset of the stimulus. The contrast of the grating stimuli was modulated so as to produce discrete counterphasing at various temporal frequencies. Except where otherwise stated, contrast of gratings was 84%. The uniform background field subtended a visual angle of 27°×20° and had a luminance of 37 cd/m^2. A well-defined fixation target was generated from a mixture of red and green light of 30%

contrast with respect to the white background field. This choice of chromatic and luminance contrast minimizes the effect of chromatic aberrations on the state of accommodation of the eye and its fluctuations and is therefore recommended for use in lengthy experiments (Corno-Martin and Denieul, 1988). In addition to temporally counterphased, Gaussian-weighted gratings of selected spatial and temporal frequencies, two other modes of temporal presentation were used: (1) *square pulsed* presentation, when the stimulus was presented at the maximum contrast for a fixed period of time; (2) *weighted pulsed* presentation, when the stimulus was presented at the maximum contrast for a fixed period of time, but in addition the rise and fall times were weighted over a range of Gaussian functions.

In both of these pulsed presentations, the duration of the stimulus at maximum contrast could be varied over a wide range. In the structureless stimulus condition, as expected, there is a mean light flux change with respect to the background level. In this condition the peak luminance was 67.7 cd/m^2. With all other stimuli, mean space-averaged flux remains unchanged during the stimulus presentation.

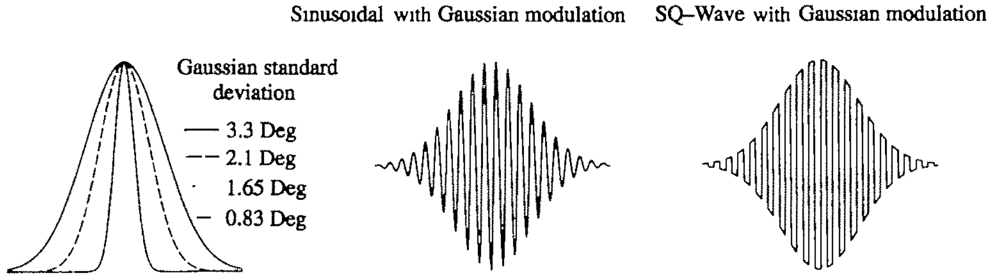
The Gaussian function in space or time is specified by its corresponding standard deviation (SD). The larger the SD the larger spread, i.e. the more gradual the change from non-stimulus to stimulus and vice versa. The spread of the stimulus in both space and time is terminated at plus and minus two SDs. For example, a spatial SD of 3° yields a circular stimulus of radius 6° For this stimulus condition, its effective size at a position 12° in the periphery is about 6° diameter as seen by the normal subject. This is because the Gaussian weighting produces a very gradual increase in contrast (or luminance in the case of structureless stimuli) towards the centre of the stimulus, with the fainter edges falling below the detection threshold. When the stimulus has no spatial structure, its appearance is that of a fuzzy 'blob', brighter at the centre and fading away at the edges.

Spatial gratings could be either square-wave or sinusoidally modulated, at a specified spatial frequency. Stimuli without spatial structure ('blobs') were generated by using a low spatial frequency component of half spatial periodicity equal to the total spread of the stimulus. Temporal modulation, similarly, could be either square-wave or sinusoidal at a specified temporal frequency. All stimuli were surrounded by a large background field and were always centred 12.5° from the fixation in the blind hemifield, the centre of the stimulus being 6.3° above the horizontal meridian.

Schematic profiles of the various stimuli are shown in Figs 1 and 2.

Procedure

A two-alternative forced-choice procedure was used throughout. Auditory beeps were used to indicate the first and the second interval of a possible stimulus presentation and the subject had to guess the interval in which the stimulus was presented. During each experimental session the set of stimulus parameters tested, such as size, spatial frequency, contrast and temporal modulation were interleaved and each stimulus was presented 30 times in the two-alternative forced-choice procedure. Fifty percent is a chance score.


Sinusoidal with Gaussian modulation
SQ–Wave with Gaussian modulation
Gaussian standard deviation
3.3 Deg
2.1 Deg
1.65 Deg
0.83 Deg

Spatial luminance modulation Spatial luminance profile Spatial luminance profile

FIG. 1. Schematic profiles of stimulus spatial distributions. All spatial displays were Gaussian-weighted, but the standard deviation and hence the size could be varied, as shown in the left-hand figure The stimuli could be either unstructured 'blobs', as shown on the left, or square-wave or sinusoidal gratings.

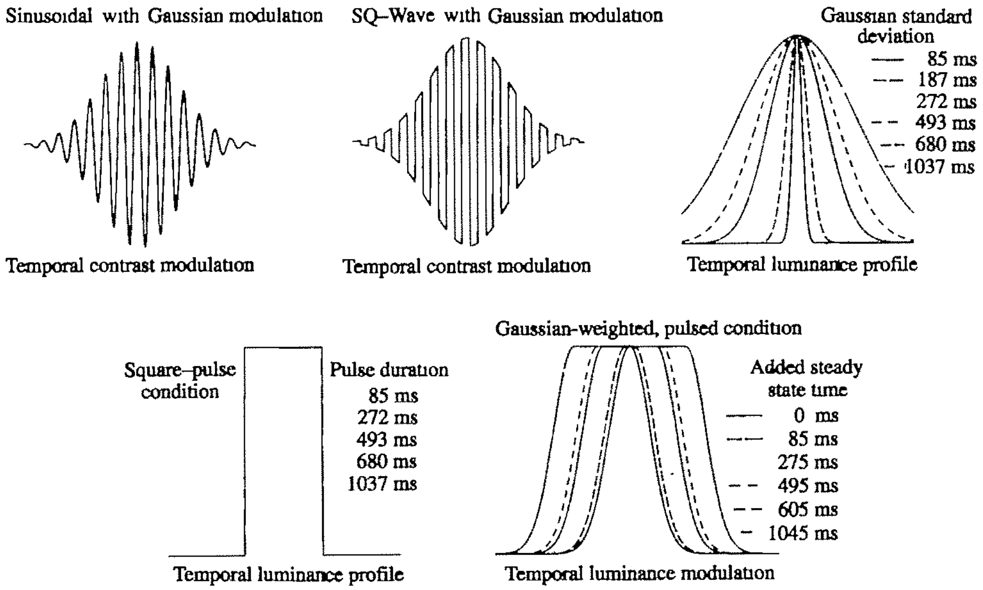

Sinusoidal with Gaussian modulation
Temporal contrast modulation
SQ–Wave with Gaussian modulation
Temporal contrast modulation
Gaussian standard deviation
85 ms
187 ms
272 ms
493 ms
680 ms
1037 ms
Temporal luminance profile
Square–pulse condition
Pulse duration
85 ms
272 ms
493 ms
680 ms
1037 ms
Temporal luminance profile
Gaussian-weighted, pulsed condition
Added steady state time
0 ms
85 ms
275 ms
495 ms
605 ms
1045 ms
Temporal luminance modulation

FIG. 2. Schematic profiles of the temporal distributions of stimuli They could be Gaussian-weighted, as shown in the top row, or pulsed for variable durations, as shown on the bottom left The duration of a temporally Gaussian-weighted stimulus could be 'stretched' as shown on the bottom right

Subject

Details of G.Y.'s visual field sensitivity, which defines a complete, homonymous hemianopia with about 3° of macular sparing have been described elsewhere (Barbur *et al.*, 1980). CT scans and the results of other psychophysical tests of his residual visual function have also been reported (Blythe *et al* , 1987; Barbur *et al.*, 1988).

RESULTS

Eye position stability

G.Y.'s eye fixations were very well maintained throughout all test conditions, with deviations of less than 40 min of arc over periods of several seconds. It could also be demonstrated during these tests, as in the past, that saccadic eye movements could be controlled by stimuli presented to his blind hemifield. Fig. 3 shows typical eye-movement responses in the absence of any warning signals when the subject was instructed to switch his fixation to any discrete stimulus presented in either his sighted or blind hemifields. A square target of 5° × 5° was employed, which approximated the effective size of typical Gaussian-weighted stimuli used in this study. The square target was centred at the same eccentricity as the Gaussian-weighted stimuli, i.e. 12.5° from the initial fixation. Fig. 4 shows only the horizontal components of G.Y.'s eye-movements in the same experiment. The data demonstrate a longer response latency following blind field stimulation with the initial saccade directed more towards the centre of the square stimulus. The results also demonstrate the subject's excellent stability of fixation (*cf* the size of the initial blobs in Fig. 3) with deviations far smaller than would be required to explain the experimental results of faulty fixation *per se*.

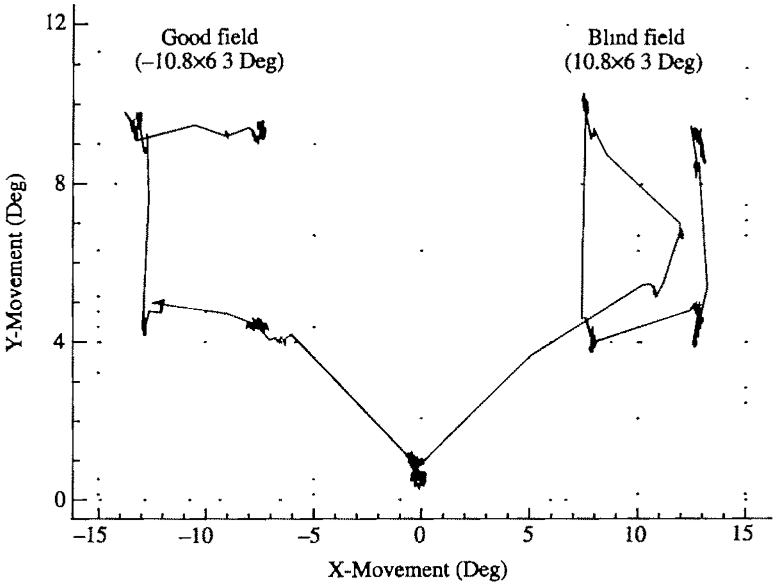


FIG 3 Record of vertical and horizontal measurements of eye movements to a stimulus presented for 6 6 s in the sighted or the blind hemifields. The initial movement is a saccade, followed by movements around the contour of the stimulus after it has been located (*see* text). The initial 'blob' at zero on the abscissa illustrates the good stability of fixation prior to the saccades The centre coordinates of the stimulus with respect to fixation was +/– 10 8° horizontally and 6.3° vertically, which made the distance from fixation to centre of stimulus 12 5°.

The effect of stimulus size

We were able to confirm Hess and Pointer's (1989) negative results using a stimulus with a spatial SD that closely matched their fixed value of 2°. Performance was at chance or near-chance for a blob with a spatial SD of 2.1° with sinusoidal temporal modulation, as they found (*see* bottom curve of Fig. 5). The next higher curve in Fig. 5 shows that a larger blob with a slightly sharper rise time (sin-wave without Gaussian temporal weighting) yielded much better performance, and increasing the slope of the temporal onset took performance to the maximum possible score of 100%.

The effect of size *per se* could be seen clearly with spatial structure and temporal onset held constant, using a square pulse presentation, and was relatively independent of pulse duration (Fig. 6). A spatial SD of 3.3° yielded performance very close to 100% correct, whereas a stimulus of SD 0.83° produced chance scores.

Effect of slope of temporal onset/offset

Confirming Hess and Pointer (1989), who used a fixed temporal SD of 250 ms throughout, we found (Fig. 7) that temporal SDs larger than approximately 250 ms, and with the same size blob they used (2°), gave chance performance. This was true even for larger stimuli (Fig. 8), with a 3.3° SD. On the other hand, Figs 7 and 8 also illustrate that as temporal SDs decreased, performance rose very sharply and reached 90% levels with temporal SDs of about 200 ms.

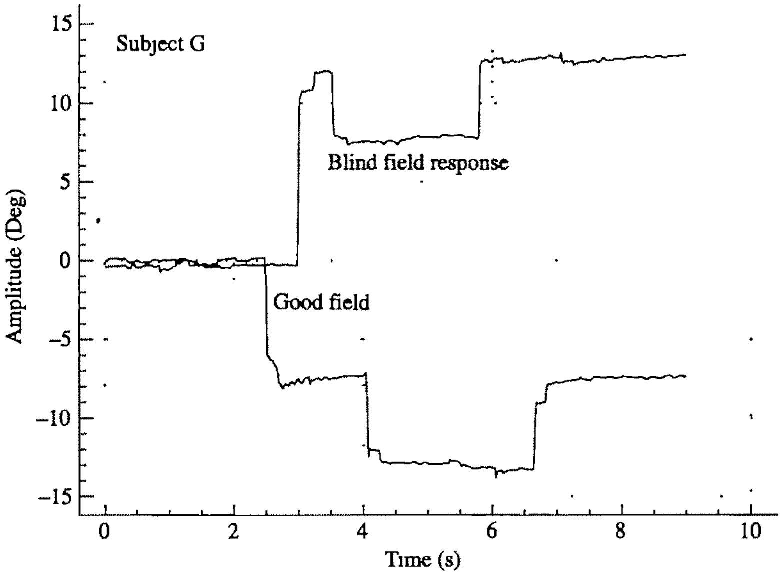


FIG. 4 Horizontal components of eye movements in the same situation as in Fig. 3 (*see* text). The latency of a saccade to the stimulus in the blind field is slower than to that in the sighted field The stability of fixation prior to the saccade is evident

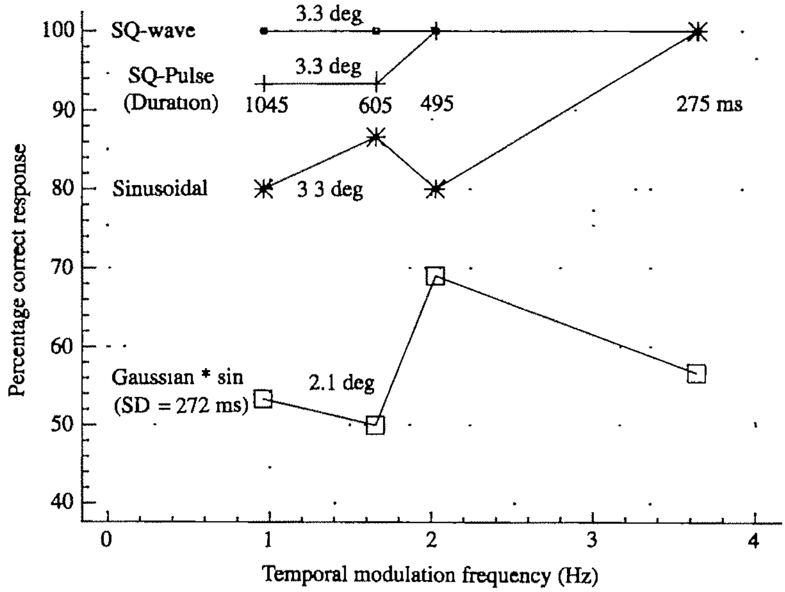


FIG 5. The effect of stimulus size and temporal modulation condition on performance. All stimuli were unstructured 'blobs'. Different durations (in ms) of single square pulses are shown near the top of the graph

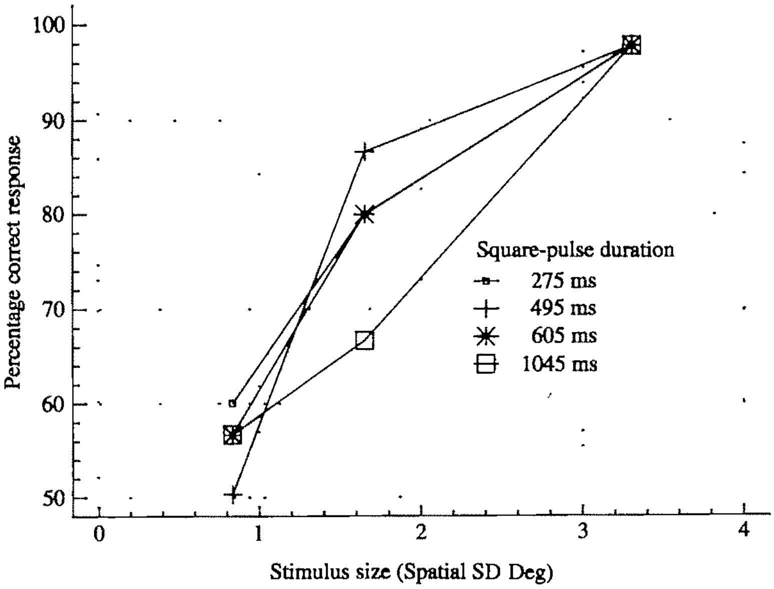


FIG 6 The effect of stimulus size for a square wave grating presented temporally as a square pulse of varying durations.

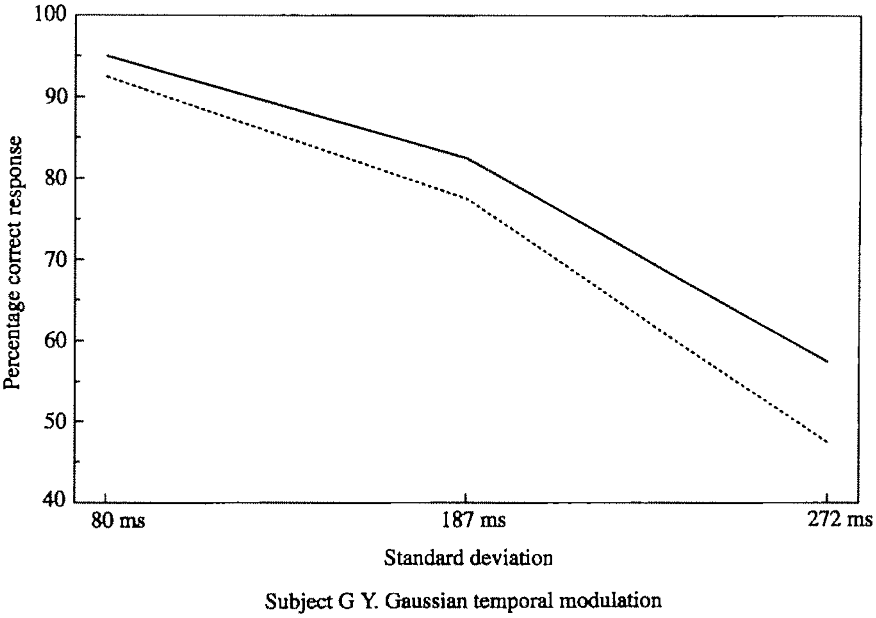


FIG 7 The effect of magnitude of temporal Gaussian SD on performance with a small uniform 'blob' (continuous line) or square-wave grating (broken line), 1 C/deg, spatial SD = 2 deg.

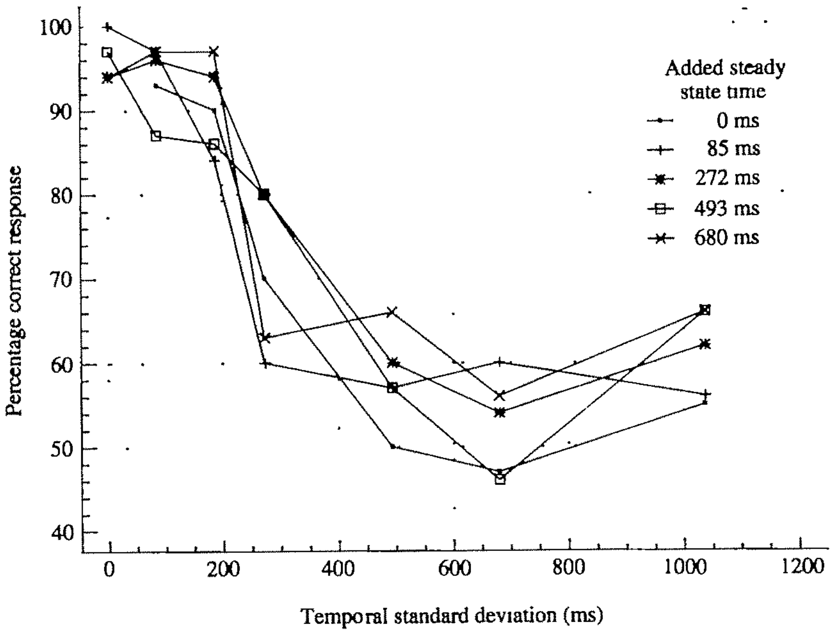


FIG. 8 The effect of magnitude of temporal Gaussian SD on performance with a square-wave grating The duration of the stimulus presentation could be 'stretched' by varying amounts. 1 C/deg SQ-wave grating, 83% contrast, spatial SD = 3.3 deg

Fig. 8 also makes it clear that the duration of the stimulus is largely irrelevant. The fact that larger temporal SDs necessarily produce stimuli of longer duration cannot be an explanation of the poorer performance with long stimuli caused, for example, by fatigue or Troxler fading. Adding even much longer durations to short temporal SDs has no deleterious effect on performance.

Fig. 9 summarizes on a single 3-D surface the relationship between steady state time (i.e. time added to that determined by the temporal SDs as such), temporal SD and performance.

Effect of temporal modulation

Frequency of modulation, as such, the only parameter varied by Hess and Pointer, was of relatively little importance within the comparatively restricted range employed here, although the highest frequency, 3.7 Hz was better than the lower frequencies. But the wave form of the temporal modulation had a strong influence. 'Blobs' with square-wave temporal modulation with Gaussian-weighted temporal onset/offset, or with square wave pulsed presentation, both generated high levels of performance (Fig. 10). In contrast, sinusoidal modulation was less effective. As seen in Fig. 10, for equal size 'blobs' there was a clear order of effectiveness of mode of temporal modulation, in decreasing order from square-wave, square-pulse, sinusoidal and sinusoidal with Gaussian onset/offset.

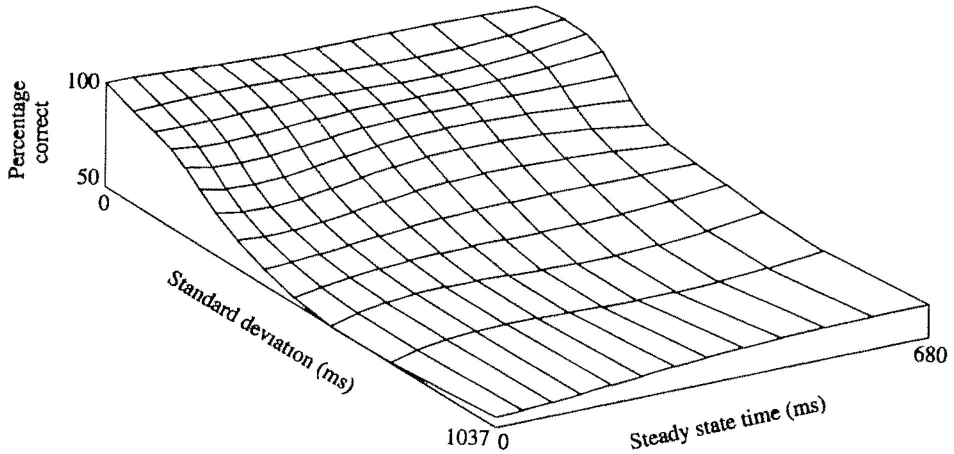


FIG. 9 Three-dimensional plot of temporal standard deviation and total added duration on performance with a square-wave grating.

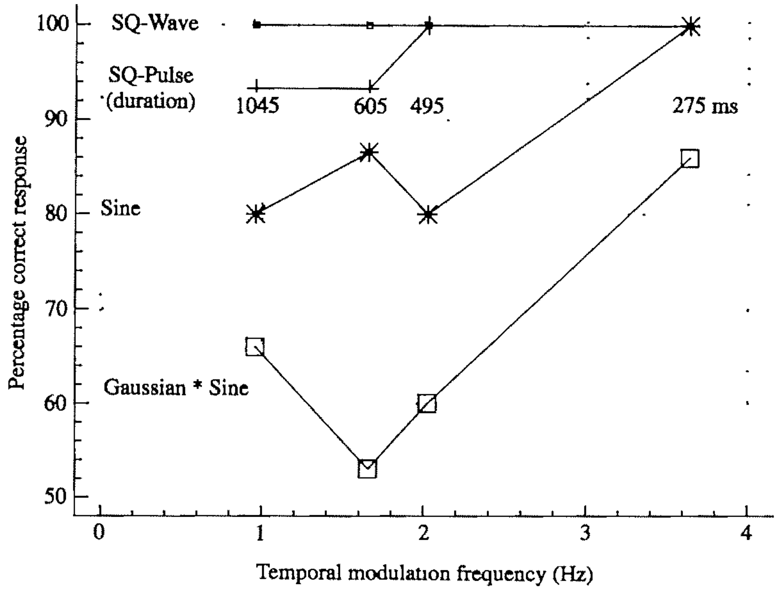


FIG. 10 The effect of different temporal modulation conditions on performance with 'blobs'. The repetitive counterphased square wave modulation yielded perfect performance. A single square pulse was also highly effective. Different durations (in ms) of single square pulses are shown near the top of the graph SD = 3.3 deg.

Effect of spatial structure

Squeezing spatial structure on to small stimuli of the size and approximate onset slope used by Hess and Pointer (1989) was ineffective. If anything, the unstructured blob was more effective than a square wave grating (Fig. 7), perhaps because the latter did

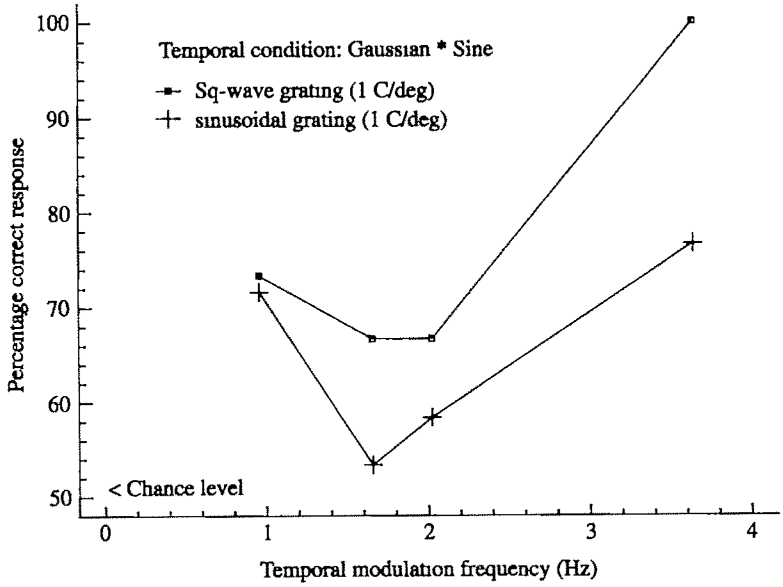


FIG. 11. Comparison of the effects of Gaussian-weighted temporal modulation on performance with a square-wave grating versus a sinusoidal grating, both of the same spatial frequency and contrast Temporal SD = 275 ms, spatial SD = 3.3 deg, 84% contrast

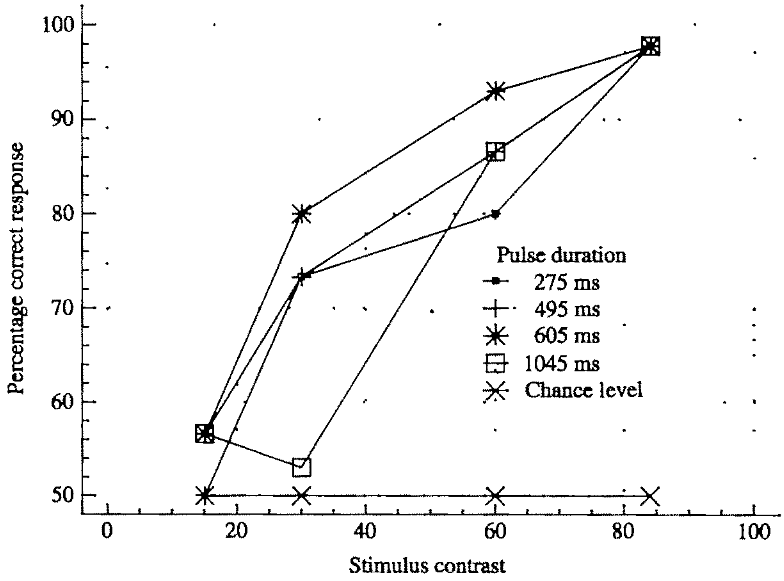


FIG. 12 Effect on performance of stimulus contrast with a square-wave grating, using square-pulsed temporal presentation with various durations of the pulse. 1 C/deg, spatial SD = 3 3 deg.

not produce a mean flux change. It will be seen that performance depended entirely on the temporal SD. This is a further replication of Hess and Pointer's (1989) findings that 'blobs' (SD of 2° blob, 272 ms temporal SD) that closely matched theirs (SD of 2°, 250 ms temporal SD), generated chance performance. But in agreement with our other findings, with faster rise times performance was very good.

But under other conditions spatial structure had an influence. With stimuli having no structure, and even with 'blobs' of our largest size, performance did not reach high levels with sinusoidal temporal modulation (with Gaussian onset/offset), although it was above chance (Fig. 11). On the other hand, with a square wave grating (Gaussian-edged), performance reached 100% correct at the highest rate of sinusoidal modulation. Similarly, with square-pulsed temporal presentation, a square-wave grating (1 C/deg) produced higher levels of performance than a sinusoidal grating of the same size (1.65°), spatial frequency and contrast (results not shown).

Effect of contrast

As expected, performance depended directly on the contrast of a grating. Fig. 12 shows the function of performance against contrast for a square wave grating (Gaussian weighted, 3.3° spatial SD), with square pulsed presentation. Depending on the pulse duration, G.Y.'s threshold lay in the region of 40% contrast. He was at chance consistently with a contrast of 15% for this stimulus, and with the contrast used in most of the tests in this study, 84%, he maintained a performance level of 98% correct over all pulse durations.

DISCUSSION

The results of the study indicate that size and temporal properties of stimuli have powerful effects on detection of stimuli in the blind field of this subject. With a Gaussian weighted spatial 'blob' of spatial SD of 2.1°, and sinusoidal temporal modulation, G.Y. was at chance or near to chance, confirming Hess and Pointer's (1989) findings with a fixed SD of 2°. But with a stimulus of spatial SD of 3.3°, and a marginally shorter temporal Gaussian SD, he could achieve 90% correct. With a square-wave grating with square-pulsed temporal presentation, he was at chance for a stimulus of spatial SD of less than 1°, but at 98% correct with a SD of 3.3°.

The effects of temporal rise and fall time were striking. With a temporal SD of 250 ms or more, G.Y. was at chance, again confirming Hess and Pointer (who used a fixed temporal SD of 250 ms). But decreasing the SD just slightly, to 200 ms (or less), yielded performance scores in the 90% range. The effect of temporal SD was independent of stimulus duration as such, beyond the duration imposed by the Gaussian rise and fall times.

When favourable size and temporal characteristics were combined, virtually perfect performance could be obtained and sustained. Thus, even if the stimulus had no spatial structure ('blob'), but was large and was presented either as a square pulse or with Gaussian square-wave modulation, scores of 90–100% were obtained over the temporal modulation range employed here. Indeed, a single on-off sharp profile already yielded performance values at ceiling, whether or not the stimulus had spatial structure. And so no further enhancement could be obtained by having square-wave temporal modulation, which of course increased the number of on-off epochs in the presentation (*see* Fig. 5).

Sharp contrast edges corresponding to square-wave gratings, under certain conditions, also increased stimulus detectability, even when the temporal modulation was not sharp, i.e. with sinusoidal modulation. Thus, a spatial Gaussian-weighted square-wave grating could yield scores of 100% correct when the sinusoidal temporal modulation was above 3 Hz, whereas a 'blob' did not reach such a high level under the same temporal modulation conditions. With G.Y. it would seem that temporal rise times less than that specified by a Gaussian SD of 250 ms make an overriding contribution to detectability, and that spatial structure becomes effective with him when it helps to increase the strength of transient signals generated by the presentation of the spatially structured pattern.

We were able to confirm Hess and Pointer's (1989) results with G.Y. when we used their stimulus parameters, but their negative conclusion applies only to their limited set of conditions, with a temporal SD of 250 ms and a spatial SD of 2°. With a relatively small decrease in temporal SD and a modest increase in spatial SD, near perfect performance was found in G.Y. As regards spatial structure, it is worth noting that they did not actually test the effects of spatial structure in the blind field, only those of temporal frequency, although the reader of their paper may assume otherwise. It would seem that they abandoned this effort after obtaining negative results in a preliminary experiment (personal communication). Had they tested spatial frequency, their results probably would have been negative, given our own findings with stimuli within the range that they used in the intact fields although, as we have seen, spatial structure had a positive influence when this range was extended.

While we can confirm Hess and Pointer's (1989) findings with their conditions, it would seem that their further conclusion, 'that using experimental conditions which would be expected to reveal even the most restricted and rudimentary spatiotemporal visual capacity, we can report no evidence for residual visual function' would appear to reflect an overgenerous expectation. One might question the implied claim that their experimental conditions were so psychophysically basic and sensitive as to uncover the most 'rudimentary' visual capacity; this would be so only given particular assumptions about the nature of visual processing. Be that as it may, it would appear that Hess and Pointer unfortunately chose parameters that were just outside the effective range. What might be optimal parameters in a psychophysical procedure for normal fields clearly do not necessarily transfer to 'blindsight' responses, nor should they be expected to do so given the findings in the literature with G.Y. and other subjects, nor given the theoretical background to such residual function. Similarly, their conclusion that, 'contrary to expectations, the contrast sensitivity associated with the subcortical projection in man cannot be measured by the standard psychophysical means used in [their] study' does not hold when parameters are used that are within the effective range (Fig. 12).

Hess and Pointer (1989) were aware that their results with G.Y. were 'seemingly at odds' with previous studies showing positive residual function in that subject, but their speculation that this was because they used a two-alternative forced-choice procedure 'whereas in previous studies the patient determined his own threshold using a method of adjustment' is not correct. It ignores other positive findings with this subject using a forced-choice procedure (Barbur *et al.*, 1980; Blythe *et al.*, 1986, 1987), as well as a much larger literature of positive findings using forced-choice psychophysical procedures with 'blindsight' subjects (Weiskrantz, 1990).

Of course, nothing can be said about the other two subjects tested by Hess and Pointer (1989), nor indeed any other 'blindsight' subject. It may or may not be the case that they would show results similar to G.Y. using stimulus parameters within the range used by us. The evidence with another thoroughly studied subject, D.B., suggests that for him temporal rise time was not an important factor (Weiskrantz, 1986, pp. 86–89), and that spatial structure was possibly of much greater importance. Again, some but not all of other patients examined for wavelength discrimination have shown positive findings (Stoerig and Cowey, 1989). Some but not all subjects tested for discrimination of directionality of movement have shown positive results (*see* Weiskrantz, 1990). The animal findings would suggest that quite fine details of just which pathways are interrupted in association with striate cortex damage will have important consequences in defining the profile of residual capacities.

G.Y. shows excellent discrimination of directionality of moving stimuli in his blind field, and also responds well to rapid transient stimuli. This suggests that area V5 (MT) may well be intact in him. In the absence of area V5, blindsight subjects may respond to movement *per se*, but not to directionality (*see* Weiskrantz, 1990, for review). Neurones in this visual association cortex continue to respond to direction of movement even with complete removal or cooling of striate cortex (Rodman *et al.*, 1989). V5 in turn receives an input from the superior colliculus, in which neurons respond selectively to flashed or fast moving stimuli, as well as an input from pre-striate cortex to which there is a small direct lateral geniculate projection. The present positive findings reinforce the possibility that G.Y.'s visual residual capacity depends on both the superior colliculus and its forward projections and/or a direct projection to pre-striate cortex and its forward projections.

The appropriate use of Gaussian-weighted, sinusoidal temporal modulation, so as to eliminate detection of onset transients may make it possible to measure true temporal and spatial response characteristics associated with residual vision in G.Y. and other subjects with damaged central visual pathways. At the same time, increasing power and resolution of brain-imaging techniques hold out the promise of relating both the empirical evidence and the theoretical considerations to neurological underpinnings of residual vision in cortically blind fields.

REFERENCES

BARBUR JL, RUDDOCK KH, WATERFIELD VA (1980) Human visual responses in the absence of the geniculocalcarine projection. *Brain*, **103**, 905–928

BARBUR JL, THOMSON WD, FORSYTH PM (1987) A new system for the simultaneous measurement of pupil size and two-dimensional eye movements. *Clinical Vision Science*, **2**, 131–142

BARBUR JL, FORSYTH PM, FINDLAY JM (1988) Human saccadic eye movements in the absence of the geniculocalcarine projection. *Brain*, **111**, 63–82.

BLYTHE IM, BROMLEY JM, KENNARD C, RUDDOCK KH (1986) Visual discrimination of target displacement remains after damage to the striate cortex in humans. *Nature, London*, **320**, 619–621.

BLYTHE IM, KENNARD C, RUDDOCK KH (1987) Residual vision in patients with retrogeniculate lesions of the visual pathways. *Brain*, **110**, 887–905.

CORNO-MARTIN F, DENIEUL P (1988) Colour stimulation and accommodation control. *Perception*, **17**, 379–380.

HESS RF, POINTER JS (1989) Spatial and temporal contrast sensitivity in hemianopia: a comparative study of the sighted and blind hemifields. *Brain*, **112**, 871–894.

Brain (1991), **114**, 2283–2301

AGEING AND PARKINSON'S DISEASE: SUBSTANTIA NIGRA REGIONAL SELECTIVITY

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SUMMARY

The micro-architecture of the substantia nigra was studied in control cases of varying age and patients with parkinsonism. A single 7 μ section stained with haematoxylin and eosin was examined at a specific level within the caudal nigra using strict criteria. The pars compacta was divided into a ventral and a dorsal tier, and each tier was further subdivided into 3 regions. In 36 control cases there was a linear fallout of pigmented neurons with advancing age in the pars compacta of the caudal substantia nigra at a rate of 4.7% per decade. Regionally, the lateral ventral tier was relatively spared (2.1% loss per decade) compared with the medial ventral tier (5.4%) and the dorsal tier (6.9%). In 20 Parkinson's disease (PD) cases of varying disease duration there was an exponential loss of pigmented neurons with a 45% loss in the first decade. Regionally, the pattern was opposite to ageing. Loss was greatest in the lateral ventral tier (average loss 91%) followed by the medial ventral tier (71%) and the dorsal tier (56%). The presymptomatic phase of PD from the onset of neuronal loss was estimated to be about 5 yrs. This phase is represented by incidental Lewy body cases: individuals who die without clinical signs of PD or dementia, but who are found to have Lewy bodies at post-mortem. In 7 cases cell loss was confined to the lateral ventral tier (average loss 52%) congruent with the lateral ventral selectivity of symptomatic PD. It was calculated that at the onset of symptoms there was a 68% cell loss in the lateral ventral tier and a 48% loss in the caudal nigra as a whole. The regional selectivity of PD is relatively specific In 15 cases of striatonigral degeneration the distribution of cell loss was similar, but the loss in the dorsal tier was greater than PD by 21%. In 14 cases of Steele-Richardson-Olszewski syndrome (SRO) there was no predilection for the lateral ventral tier, but a tendency to involve the medial nigra and spare the lateral. These findings suggest that age-related attrition of pigmented nigral cells is not an important factor in the pathogenesis of PD.

INTRODUCTION

The concept of neuronal loss occurring with advancing age was first proposed by Hodge (1894). For the substantia nigra this was confirmed by three morphometric studies, which found losses of 38%, 48% and 36% between the age of 20 and 90 yrs (Hirai, 1968; McGeer *et al.*, 1977; Mann *et al.*, 1984). This has also been verified by biochemical studies. Riederer and Wuketich (1976) found a 13% reduction of caudate dopamine per decade; Carlsson *et al.* (1984) observed a non-linear decline of striatal dopamine with little loss until the age of 60 yrs followed by a dramatic fall thereafter; Scherman *et al.* (1989) assessed striatal dopamine levels by measuring the binding of alpha-dihydrotetrabenazine, a ligand of the vesicular monoamine transporter and found a linear decline of under 10% per decade. Neuronal loss in normal ageing is not sufficient to cause PD. In PD, there is a presymptomatic phase and clinical signs do not appear until 50% of nigral neurons and 80% of striatal dopamine is lost (Marsden, 1990).

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The Lewy body is a hyaline neuronal inclusion body, which is always present in PD (Gibb and Lees, 1988). Forno (1969) has proposed that incidental Lewy body cases are representative of the presymptomatic phase of PD. These are individuals who die without a history of parkinsonism or dementia, but who are found to have Lewy bodies at autopsy. However, it has been suggested that Lewy bodies as an incidental finding are a feature of normal ageing without any additional nigral cell loss (Hansen *et al.*, 1990).

Similarities have been drawn between senility and PD on the grounds of shared clinical features (Teräväinen and Calne, 1983; Evarts *et al.*, 1981) and enhancement of the long latency stretch reflex (Tatton and Lee, 1975; Evarts *et al.*, 1979). Moreover, ageing has been considered to play an important role in the pathogenesis of PD. It has been suggested that PD is a form of accelerated ageing (Mann and Yates, 1983; Barbeau, 1984) or alternatively that PD is a biphasic illness (Riederer and Wuketich, 1976; Calne *et al.*, 1986; Mattock *et al.*, 1988). The first phase, an acute illness early in life sharply depletes neuronal reserves, but not enough to cause clinical parkinsonism. This deficit is then unmasked by further losses due to normal ageing over the following 20 to 30 yrs. Evidence cited for this theory is the finding of subclinical nigral damage in methyl-phenyl-tetrahydropyridine (MPTP) toxicity (Calne *et al.*, 1985) and the frequent lag between encephalitis lethargica and the onset of parkonsonism (Duvoisin and Yahr, 1965).

The substantia nigra is an anatomically heterogeneous nucleus with regional variations in striatal projections and distribution of histochemical markers. Evidence suggests that degenerative diseases of the nigra demonstrate regional selectivity and this may be important in the pathogenesis of disease. In PD, neuronal loss is most severe in its caudal and ventrolateral parts (Hassler, 1938). In striatonigral degeneration (SND) the pattern of cell loss has been variously described as medial (Andrews *et al.*, 1970), lateral (Jellinger and Danielczyk, 1968; Sharpe *et al.*, 1973; Trotter, 1973; Buonanno *et al.*, 1975; Bannister *et al.*, 1981), central (Takei and Mirra, 1973; Sung *et al.*, 1979), dorsolateral (Borit *et al.*, 1975) and affecting the ventral and middle parts (Rajput *et al.*, 1972). The nigral distribution of Steele-Richardson-Olszewski syndrome (SRO) has been described as lateral (Steele *et al.*, 1964), ventromedial (Jellinger, 1971) and non-selective (Anzil, 1969). In ageing, the distribution of nigral cell loss has not been studied.

We present the first regional semi-quantitative study to be based on division of the substantia nigra by defined cell groups. Using this technique we studied the regional selectivity of normal ageing, incidental Lewy body cases, PD, SND and SRO.

MATERIALS AND METHOD

Two hundred and five control cases without a history of parkinsonism or dementia were collected prospectively over a 5 yr period by several hospital pathology departments through the auspices of the UK Parkinson's Disease Society Brain Bank and for 1 yr by the Department of Pathology, Innsbruck, Austria. All cases were used to calculate the prevalence of incidental Lewy bodies, but only a proportion were suitable for morphometric study. During the same period, 50 PD cases, 22 SND cases and 6 SRO cases were also collected. The brains were divided midsagittally: one-half immersion fixed in 10% buffered formalin for a period of 5 wks and the other frozen at −70°C. Multiple blocks were taken for microscopic examination. Pathological diagnosis of PD, SND and SRO was made on the distribution of cell loss and in the case of PD and SRO the presence and distribution of Lewy bodies and neurofibrillary tangles, respectively. A number of control cases had Lewy bodies in a distribution similar to PD and formed the incidental Lewy body group.

The anatomy of the substantia nigra was comprehensively studied by Hassler (1937) who identified around

50 neuronal groups. Hassler used the coronal plane perpendicular to the axis of Forel rather than the more contemporary transverse plane perpendicular to the axis of Meynert. For this study, nigral anatomy was reappraised in 5 control cases by examining 20 μ sections spaced every 250 μ to 500 μ throughout the nigra and stained with luxol fast blue/cresyl violet and cresyl violet alone Blocks were taken in the transverse plane, but in one whole brain, one side of the nigra was blocked in the coronal plane for comparison

Unlike Hassler who divided the nigra into separate oral and caudal parts, we found that the nigra is organized into three tiers: pars reticulata, ventral pars compacta and dorsal pars compacta, *see* Fig. 1. The tiers are staggered and the ventral tier is mainly confined to the caudal nigra arising orally within the pars reticulata Within the two tiers of the pars compacta we were able to confirm Hassler's groups. However, we found that the oral and caudal groups were continuous forming parallel columns along the length of the tier, *see* Fig. 2. As a result of this parallel arrangement there was little difference in the cross-sectional configuration of the neuronal groups between the coronal and transverse planes, which are angled by 30° – 40°. However, the levels of sampling within the nigra were different In the transverse plane compared with the coronal plane, the medial groups were sampled at a higher level and the lateral and dorsal groups at a lower level.

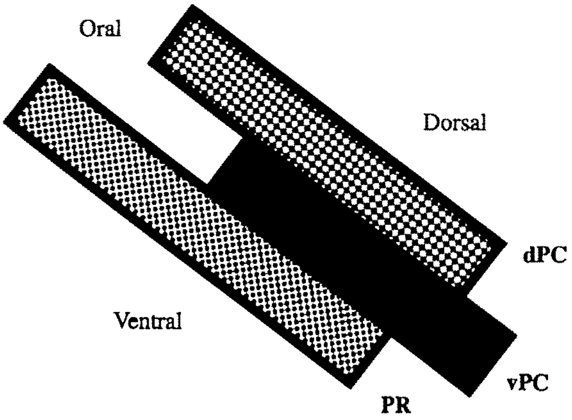

FIG 1. *Substantia nigra tiers.* Sagittal representation of the substantia nigra. PR = pars reticulata (dots) vPC = ventral tier pars compacta (black). dPC = dorsal tier pars compacta (crosses).

An alternative system of classification of the pars compacta groups is proposed taking into account the concept of tiering and Hassler's original work. Each group is abbreviated to two letters corresponding to the tier and division and one letter in brackets corresponding to the group. The pars compacta is divided into two tiers: ventral – v, and dorsal – d. The dorsal tier has three divisions: medial – dm, lateral – dl and pars lateralis – pl. The ventral tier has two divisions· medial – vm, and lateral – vl. Each division has 1 to 4 groups· medial – (m), intermediate – (i), lateral – (l) and eutopic – (e). This classification is compared with Hassler's in Table 1. The group vl(e) corresponds to Hassler's eutopic group eJ and has been included with vl for the sake of simplicity. A number of Hassler's nigral groups correspond to the ventral tegmental area and the retrorubral area and have not been included.

A single 7 μ section of the caudal nigra stained with haematoxylin and eosin was used for morphometry. At this level, the IIIrd nerve fascicles demarcate the ventral tegmental area from the nigra (Olszewski and Baxter, 1954). Criteria for selecting a consistent level were defined on the basis of neuronal groups and their complementary nerve fibre fields as described by Hassler and are as follows· *medially,* where the IIIrd nerve fascicles divide the nigra from the ventral tegmental area above the decussation of the superior cerebellar peduncle between the main bulk of the Hassler's oral nerve fibre field rab, and the caudal field v, *centrally,* at the level of Hassler's neuronal group hj and its distinctive nerve fibre field; *laterally,* at the point where the striatonigral pathway (Hassler's nerve fibre field K) is well formed and oral enough to be distant from the medial lemniscus and caudal enough to be below neuronal group vl(e).

In the pathological cases, it was still possible to recognize neuronal groups by the remaining nerve cells,

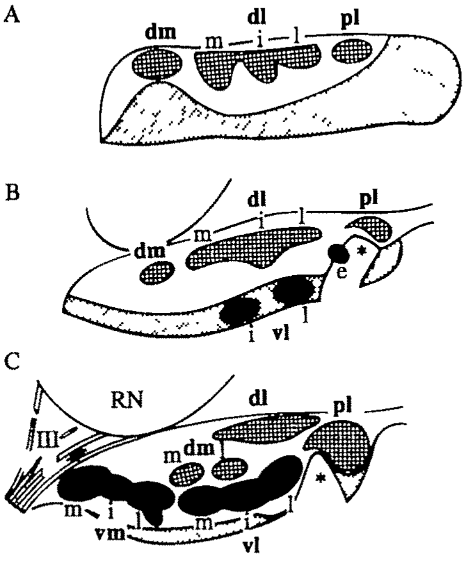

FIG. 2. *Substantia nigra groups.* The substantia nigra in the transverse plane perpendicular to the axis of Meynert: A, oral nigra; B, mid nigra; C, caudal nigra. Medial nigra left of page and lateral nigra right of page Tiers coded according to Fig. 1. Bold letters correspond to the tier and the division and regular letters to group, *see* text for explanation. IIIrd nerve fascicles. RN = red nucleus. *Putaminonigral pathway (Hassler's nerve fibre field K).

TABLE 1. COMPARISON PRELIMINARY ANATOMICAL STUDY WITH THE WORK OF HASSLER (1937)

Fearnley and Lees			*Hassler's groups*	
Tier	*Division*	*Group*	*Oral*	*Caudal*
v	vm	(m)		Spvm
		(i)		Spvi
		(l)		Spvl
	vl	(m)		Spev
		(i)	Saivz	Spez
		(l)	Saivl	Sped, Spedd
		(e)		eJ
d	dm	(m)	Sam alpha*[1] ak*[2]	Spzv*[3]
		(l)		Spzz
	dl	(m)	Saim	Spdm
		(i)	Saiz	Spdi
		(l)	Sail	Spdd
	pl	—	Sal	Spcd

Nomenclature (Fearnley and Lees): v = ventral, d = dorsal, m = medial, i = intermediate, l = lateral, e = eutopic * Order of appearance from oral (1) to caudal (3).

nerve fibre fields, and condensation of glia For example, even when vl has no pigmented neurons its outline is recognizable by a strip of closely packed astrocytes.

As there was no landmark laterally when cutting the midbrain many of the blocks were tilted and unsatisfactory for morphometry. The proportion of cases that were suitable was: 36/192 controls without LBs, 6/13 controls with LBs (incidental LB cases), 20/50 PD cases, 15/22 SND cases and 4/6 SRO cases.

Discrepancies between these proportions arose from chance and the fact that the brains had been cut by five different persons. Archival material at the Institute of Psychiatry, London, yielded a further 10 SRO cases and 1 incidental Lewy body case suitable for morphometry

The substantia nigra of each case was divided into 6 morphometric regions (Fig. 3), by marking the coverslip of the slide with a 0.13 mm Rotring pen under 40 and 100× magnification. The morphometric regions (capital letters) differed from the anatomical groups in two instances. vl(m) was divided off from vl and counted separately as VI. The purpose in selecting this area for particular attention was to test further whether pathological processes respected the boundaries of the major nigral divisions. dl(l) was included in DM for ease of marking. Slides were coded so that the morphometrist was unaware of the patient's age. Pigmented neurons in each region were counted twice using alternately the cell body and nucleolus as the counting unit for the purposes of comparison and validation. The nucleolus has the advantages of good contrast with the rest of the cell, small size and uniform shape. However, a potential disadvantage in the substantia nigra is obscuration by pigment. The total count (number of pigmented neurons in a single section of the caudal nigra) was calculated by summating the regional counts. The slide was then remarked and recounted. Counting was performed under 400× magnification using an eyepiece graticule and parallel sweeps of the microscope stage. No corrections were made for split cell error. The following areas were not counted: pars reticulata; ventral tegmental area; retrorubral area and nucleus peripeduncularis.

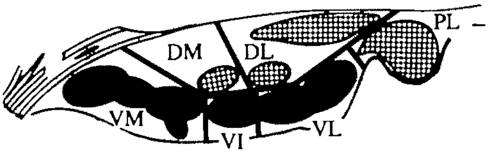

FIG. 3. *Morphometric regions.* Taken at the level of the caudal nigra, Fig. 2c. Dorsal tier: medial part (DM), lateral part (DL) and pars lateralis (PL) Ventral tier: medial part (VM) and lateral part (VI-intermediate and VL)

Regression equations were calculated for the control regional and total counts vs age. The pathological cases including the incidental Lewy body cases varied in age. In order to assess the neuronal loss due to the pathological process separate from losses due to ageing it was necessary to correct the regional and total counts for age. For each of the pathological cases predicted control regional and total counts were calculated from the corresponding regression equations (Table 4). The pathological count was then expressed as a percentage of the predicted control count. Alternatively, cell loss was estimated by expressing the pathological count as a percentage of an age-matched control count. Significance was tested using Student's *t* test. Figures preceded by ± represent one standard deviation.

RESULTS

The results of the nucleolus and cell body counts were comparable except that the cell body counts reached a greater level of statistical significance due to the larger numbers counted and only data from cell body counting will be presented. Obscuration of the nucleolus by pigment was not a problem at a section thickness of 7 μ and using a magnification of 400×. Variation between consecutive counts (including re-marking of the slide) was <5%. The average neuronal loss in the incidental Lewy body and parkinsonian groups was estimated by using age-adjusted counts expressed as a percentage of the predicted control and alternatively by comparing uncorrected counts directly with age-matched controls. Both methods gave similar results with no significant difference. No difference was found between VI and VL in normal ageing or disease. Uncorrected and age-adjusted cell body counts are listed in Tables 2 and 3, respectively.

TABLE 2 AVERAGE CELL BODY COUNTS

Age/sex	*Dur.*	*VM*	*VI*	*VL*	*DM*	*DL*	*PL*	*Total*
(A) Control								
21M		206	45	200	74	76	91	692
22F		184	54	216	93	108	137	692
29M		192	47	198	72	82	104	695
31M		171	46	178	83	88	91	657
44M		146	44	206	64	58	115	633
47M		176	44	200	48	50	65	583
53F		136	43	188	60	94	92	613
54M		184	45	181	87	84	111	692
55M		188	41	178	84	90	72	653
56F		172	47	188	75	88	88	658
58M		140	37	184	71	69	87	588
58M		155	37	167	60	58	67	544
60F		152	42	215	61	76	96	642
61M		150	40	177	69	65	86	587
61F		177	46	173	50	58	81	585
65F		88	34	147	32	53	49	403
65M		131	22	201	50	50	64	518
69F		188	51	187	68	96	112	702
70F		72	20	146	32	72	64	406
70M		152	48	200	71	44	100	615
71M		158	41	190	75	48	46	558
75F		124	39	170	50	37	73	493
75M		109	46	182	45	57	65	504
77M		85	40	160	30	29	46	390
78M		104	36	183	37	58	85	503
79M		132	49	180	58	44	57	520
80F		148	40	179	60	63	66	556
81F		139	42	152	68	83	59	543
81M		116	33	175	39	55	30	448
84F		193	40	190	61	62	102	648
85F		168	40	199	64	62	83	616
86M		120	37	176	45	39	54	471
87M		114	46	206	42	48	84	540
89M		139	35	192	50	59	103	578
91F		122	41	159	32	39	33	426
91M		90	42	167	30	35	30	394
(B) Incidental Lewy bodies								
65F		152	18	99	55	55	64	443
75M		156	22	113	55	48	65	459
78M		118	11	76	50	48	56	359
80F		132	20	94	51	47	57	401
80M		114	17	63	41	44	29	308
81F		143	24	72	53	51	61	404
82F		127	17	81	50	41	48	364
(C) Parkinson's disease								
68M	1½	133	24	78	67	56	45	403
62F	2	67	5	30	34	32	66	234
74M	6	36	8	22	39	38	49	192
81M	6	123	17	49	43	32	31	295
73M	10	70	16	23	38	31	34	212
73F	–	132	5	13	54	34	53	291
73M	11	8	2	11	20	23	33	97
83F	12	21	2	3	29	23	14	92

Age/sex	*Dur.*	*VM*	*VI*	*VL*	*DM*	*DL*	*PL*	*Total*
76F	13	16	0	0	22	16	24	78
80M	15	19	0	10	14	12	27	83
78M	20	30	0	0	27	41	26	124
80M	–	33	0	8	34	30	35	140
78M	15	33	0	2	16	13	4	68
71F	17	8	1	13	18	19	7	66
71M	18	9	0	4	18	22	25	78
87F	25	3	0	0	31	17	19	70
82F	29	2	0	0	12	11	12	37
64F	38	12	0	0	18	9	8	47
74M	–	12	0	0	15	15	15	57
77M	–	6	2	7	25	17	18	75
(D) Striatonigral degeneration								
68M	2	14	0	0	10	9	3	36
67F	3	66	5	11	25	15	16	138
51M	4	26	1	2	20	12	15	76
56F	5	10	0	0	4	2	2	18
61M	5	42	0	3	27	27	8	107
66M	5	44	3	4	33	11	24	119
72F	5	82	17	14	39	19	18	189
43M	6	13	0	2	4	5	8	32
62M	6	48	4	1	26	5	4	88
74F	6	19	0	1	16	20	13	69
65M	7	8	0	11	14	34	30	97
64F	8	57	5	3	17	10	13	105
78M	8	74	2	4	31	29	34	174
59F	10	14	0	0	5	4	3	26
61F	10	3	0	1	7	5	4	20
(E) Steele-Richardson-Olszewski syndrome								
70M	2	32	8	46	15	14	37	152
59F	4	34	9	66	11	24	34	178
59M	4	14	8	92	10	12	16	152
68M	4	32	10	39	11	15	20	127
79F	4	15	6	22	4	7	25	79
66F	5	8	2	20	9	8	2	49
75M	5	31	5	20	11	3	26	96
79F	5	3	2	13	3	5	5	31
55F	6	3	2	15	6	8	15	49
67F	6	18	10	32	7	6	29	102
71M	6	10	4	37	10	14	25	100
72F	8	11	10	63	7	12	32	128
66F	9	28	11	22	12	8	4	85
68F	–	9	4	17	15	9	28	82

Control cases and ageing

The 36 control brains suitable for morphometry ranged in age from 21 to 91 yrs. Regression equations were calculated for the regional and total neuronal counts vs age, *see* Table 4. There was a linear decline with advancing age in both the total count of the caudal nigra (Fig. 4) and the regional counts. The regression equations were then used to calculate the neuronal loss between the age of 20 and 90 yrs for the caudal nigra and each region. The total count fell 33% (4.7% per decade). Regionally there was sparing of VI/VL with 2.5 to 3 times greater loss in the other regions (Fig. 5B). The

TABLE 3 AVERAGE AGE-ADJUSTED CELL BODY COUNTS (PERCENT OF PREDICTED CONTROL)

Age/sex	*Dur.*	*VM*	*VI*	*VL*	*DM*	*DL*	*PL*	*Total*
(A) Incidental Lewy bodies								
65F	−1.6	104	44	54	94	87	82	78
75M	−2.8	115	55	63	104	86	92	86
78M	0.1	89	28	43	78	87	82	68
80F	−1.4	102	51	53	102	87	85	77
80M	1.9	88	43	36	82	81	43	59
81F	−1.7	111	61	41	108	97	92	79
82F	−0.4	99	43	46	103	78	73	71
(B) Parkinson's disease								
Mild cases								
68M	1½	93	59	42	118	92	60	72
62F	2	45	12	16	57	49	83	40
74M	6	26	20	12	73	67	69	36
81M	6	95	43	28	87	61	47	57
73M	10	51	40	13	71	54	48	39
73F	–	96	12	7	100	59	74	54
Moderate cases								
73M	11	6	5	6	37	40	46	18
83F	12	17	5	2	60	45	22	18
76F	13	24	0	0	40	29	35	15
80M	15	15	0	6	28	23	41	16
78M	20	23	0	0	53	75	38	24
80M	–	25	0	5	68	56	53	27
Severe cases								
78M	15	25	0	1	31	24	6	13
71F	17	6	2	7	33	32	10	12
71M	18	6	0	2	31	37	34	14
87F	25	2	0	0	68	35	31	14
82F	29	2	0	0	25	21	19	7
64F	38	8	0	0	31	14	10	8
74M	–	9	0	0	28	26	21	11
77M	–	5	5	4	46	31	26	14
(C) Striatonigral degeneration								
68M	2	10	0	0	18	15	4	6
67F	3	46	12	6	44	23	20	25
51M	4	16	2	1	30	17	17	12
56F	5	6	0	0	6	3	2	3
61M	5	28	0	2	44	41	10	18
66M	5	30	7	2	57	18	31	21
72F	5	61	42	8	70	32	25	35
43M	6	8	0	1	6	7	9	5
62M	6	32	10	0	43	8	5	15
74F	6	14	0	1	30	35	18	13
65M	7	6	0	6	24	54	39	17
64F	8	39	12	2	29	16	17	18
78M	8	56	5	2	60	53	50	33
59F	10	9	0	0	8	6	4	4
61F	10	2	0	0	12	8	5	4
(D) Steele-Richardson-Olszewski syndrome								
70M	2	23	20	25	27	25	50	27
59F	4	22	22	36	18	36	42	30

Age/sex	*Dur.*	*VM*	*VI*	*VL*	*DM*	*DL*	*PL*	*Total*
59M	4	9	19	49	16	18	20	26
68M	4	23	25	21	20	25	27	23
79F	4	11	15	12	8	13	38	15
66F	5	6	5	11	16	13	3	9
75M	5	23	13	11	21	5	37	18
79F	5	2	5	7	6	9	7	6
55F	6	2	5	8	9	12	18	8
67F	6	12	25	17	12	10	38	18
71M	6	7	10	20	18	24	34	18
72F	8	8	25	35	17	21	45	24
66F	9	19	27	12	21	13	5	15
68F	–	6	10	9	26	15	37	15

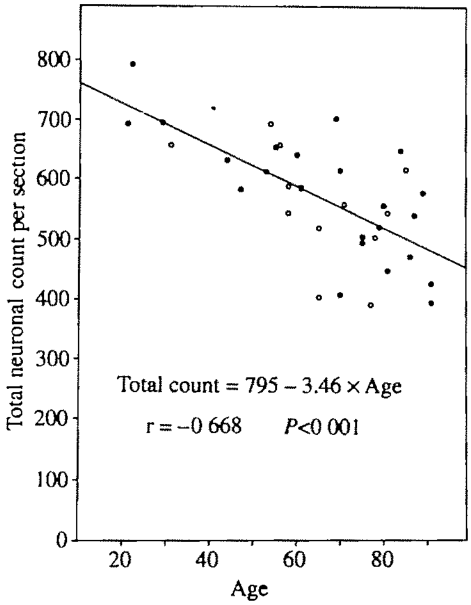

FIG 4 *Ageing and the substantia nigra.* The total neuronal count equals the number of pigmented cell bodies in one section of the caudal substantia nigra.

range of counts within each decade increased with consecutive decades suggesting variability in the effects of ageing. Qualitatively, DM, DL, PL and less frequently VM were the most heavily pigmented regions within the nigra.

Incidental Lewy body cases

Incidental Lewy bodies were found in 13 of the 205 control cases. In no case was there a history of parkinsonism or dementia. The incidental cases ranged in age from 46 to 90 yrs with a mean age of 76 ± 12. The age specific prevalence increased with age to 12% over 80 yrs (Table 5).

There was a significant reduction in the total count ($P < 0.01$) of the 7 incidental cases suitable for morphometry compared with age-matched controls. Regionally, there was only significant loss in VI/VL ($P < 0.001$). The average reduction in the total count was 27 ± 17% and in VI/VL 52 ± 9% (Fig. 5c).

TABLE 4. CONTROL CASES AGE-RELATED NEURONAL ATTRITION BETWEEN THE AGE OF 20 AND 90 YRS

	*Attrition***	*Regression equation (count = b−m·age)*		*Correlation*	
Counts	*between 20 and 90 yrs*	*b*	*m*	*r*	*P<*
Region*					
VM	38%	214.0	1.050	−0.580	0.001
VI	18%	49.0	0.122	−0.339	0.05
VL	14%	206.4	0.356	−0.387	0.02
DM	48%	95.6	0.572	−0.630	0.001
DL	48%	104.6	0.632	−0.619	0.001
PL	46%	125.5	0.735	−0.552	0.001
Total***	33%	794.8	3.462	−0.668	0.001

**See* Fig. 3 for the location of the region within caudal nigra. **Calculated from regression equation.

$$\text{attrition} = (\text{count}_{20} - \text{count}_{90})/\text{count}_{20} \cdot 100\%$$
$$= (70 \cdot m)/(b - 20 \cdot m) \cdot 100\%$$

b = intercept, m = slope, r = correlation coefficient.

***Caudal substantia nigra

Parkinson's disease cases

There was a significant reduction in both the total and regional counts of the PD cases compared with controls ($P < 0.001$). The average percent losses were maximal in VI/VL followed by VM and then the dorsal regions DM, DL and PL, *see* Fig. 5D.

The 20 PD cases ranged in age from 62 to 87 yrs (mean 75 ± 6). In 16 cases the onset of symptoms was well documented with an average age of 60 ± 11 yrs and an average duration of 15 ± 10 yrs. There was no correlation between age and symptom duration or between age and neuronal count. However, there was good correlation between symptom duration and neuronal loss ($P < 0.001$). There was an exponential decline in the total and regional age-adjusted counts with increasing symptom duration (Figs. 6, 7), so that losses were greatest in the beginning of the disease and then tailed off as it progressed. In the first decade from the onset of neuronal loss, there was a 45% fall in the age-adjusted total count, ten times greater than the rate of loss that could be accounted for by ageing. Similar results were found using uncorrected counts.

Presymptomatic phase of Parkinson's disease

The presymptomatic phase was taken as the period from the onset of neuronal loss to the onset of symptoms. It was found to be 4.7 yrs using the equation from Fig. 6 for the total age-adjusted count in PD. During this period neuronal loss due to PD, excluding age-related loss, was 31% for the total count and 64% for the regional VL count. The loss due to ageing was calculated from the control regression equations of Table 4 over the interval from both birth to onset of neuronal loss (mean age 55 yrs) and birth to the onset of symptoms (mean age 60 yrs). The average loss due to ageing was 24−26% for the total count and 10−11% for the regional VL count. The average combined loss at the onset of symptoms was 48% for the total count and 68% for the VL regional count.

To test whether any of the incidental Lewy body cases might have had undetected

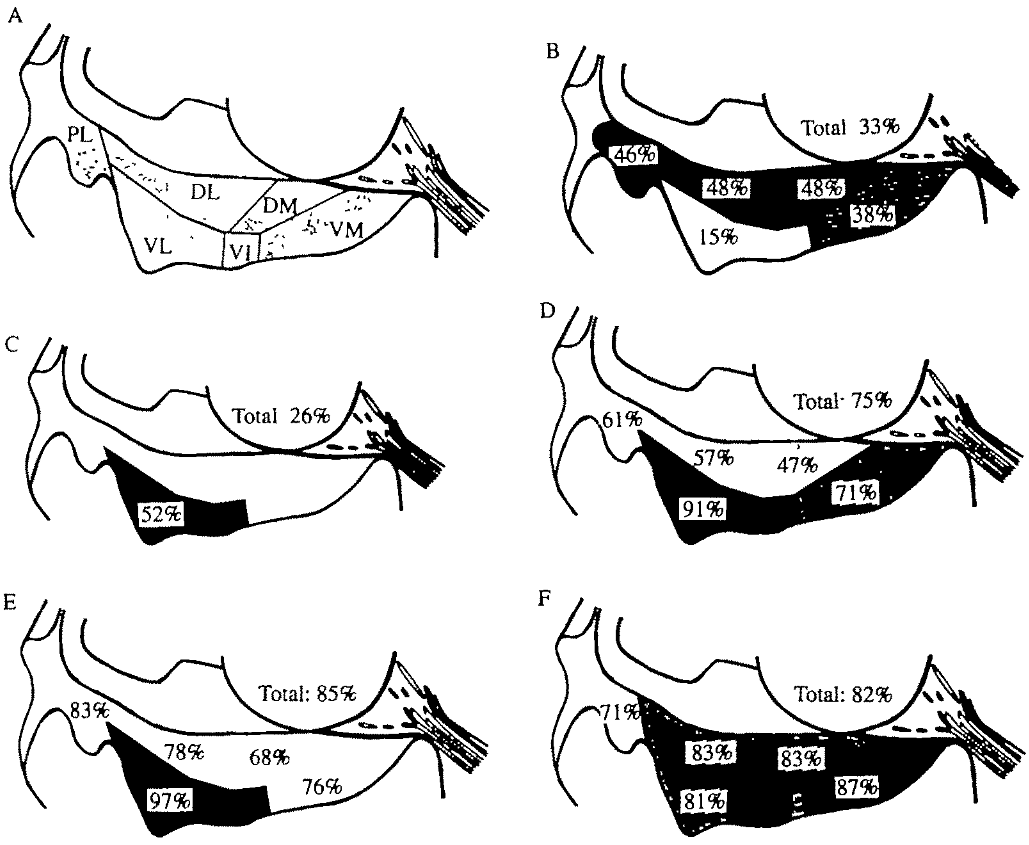

FIG 5 *Substantia nigra regional losses in ageing and disease.* A, normal anatomy, B, ageing*, C, incidental Lewy body cases**; D, Parkinson's disease**, E, striatonigral degeneration**; F, Steele-Richardson-Olszewski syndrome** A continuous border between two regions indicates a significant difference in the percent neuronal loss *Percentage loss between the age of 20 and 90 yrs **Average percentage loss in cases studied.

TABLE 5 AGE SPECIFIC PREVALENCE OF INCIDENTAL LEWY BODIES

Age	*n*	*Percent*
<20	0/2	
20–29	0/6	
30–39	0/6	
40–49	1/7	3.7
50–59	0/20	
60–69	2/51	3.9
70–79	3/56	5.4
80–89	6/49	12.2
90–99	1/8	12.5

parkinsonism during life individual total counts were scrutinized. From each the symptom duration was calculated using the equation of Fig. 6. Using this analysis, 1 case might well have been symptomatic for a duration of 2 yrs. Another case may have been

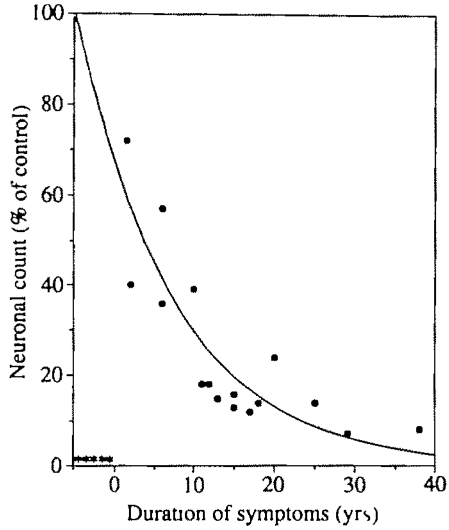

FIG 6. *Parkinson's disease.* Total age adjusted count vs symptom duration

*****Presymptomatic phase: duration 4.7 yrs.

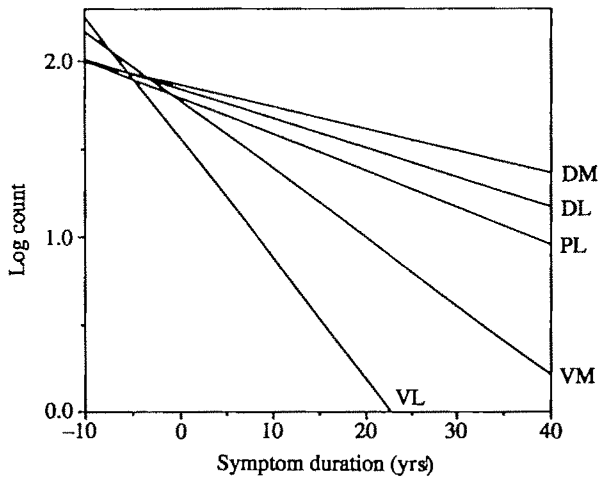

FIG 7. *Parkinson's disease.* Logarithm of regional age adjusted counts vs symptom duration

Region	*Regression equation*	*r*	*P*
VM	Log (count) = 1.78−0.0393 duration	0.740	< 0.01
VL	Log (count) = 1.57−0.0685 duration	0.787	< 0.001
DM	Log (count) = 1.87−0.0128 duration	0.618	< 0.02
DL	Log (count) = 1.84−0.0169 duration	0.742	< 0.001
PL	Log (count) = 1.80−0.0211 duration	0.637	< 0.01

marginally symptomatic with a symptom duration of 1 mth. Both these cases would have been aged 78 yrs at the onset of symptoms.

Topographical progression of Parkinson's disease

The topographical progression in the nigra of PD was studied by including the incidental Lewy body cases, as representative of the presymptomatic phase, and dividing the PD

TABLE 6 PARKINSON'S DISEASE CASES

Group	No.	Total count (age adjusted)	Clinical details	
			*Duration***	*Stage*,***
+ mild	6	> 35%	5±3.5	3.4
++ moderate	6	< 35%	14±3.6	4.4
+++ severe	8	< 15%	24±8.8	4.8
Significance of differences				
Mild–moderate		$P < 0.001$	$P < 0.01$	$P < 0.05$***
Moderate–severe		$P < 0.02$	$P < 0.05$	n.s

* Hoehn and Yahr (1967) ** Where available *** Wilcoxon rank sum test.

cases into mild, moderate and severe groups depending on the total count (*see* Table 6). Fig. 8 illustrates the staggering of regional neuronal loss, starting in VI/VL and then spreading to the other regions and in particular VM.

Striatonigral degeneration cases

The 15 SND cases ranged in age from 43 to 78 yrs (mean 63±9) and the average symptom duration was 6±2 yrs. Compared with age-matched controls there was a significant reduction in both the total and regional counts ($P < 0.001$). The average percent neuronal loss is shown in Fig. 5E. There was no significant difference between the average total count of the SND cases and the PD cases. However, loss in the dorsal tier (DM, DL and PL combined) was greater than PD by 21% ($P < 0.01$). When compared with the moderate/severe cases of PD (average total loss 85%), the SND cases had a smaller loss in VM of around 12% ($P < 0.05$).

Steele-Richardson-Olszewski syndrome

The 14 SRO cases ranged in age from 55 to 79 yrs (mean 68±7) and the average symptom duration was 5±2 yrs. Compared with age-matched controls there was a significant reduction ($P < 0.001$) in both the total and regional counts. The average

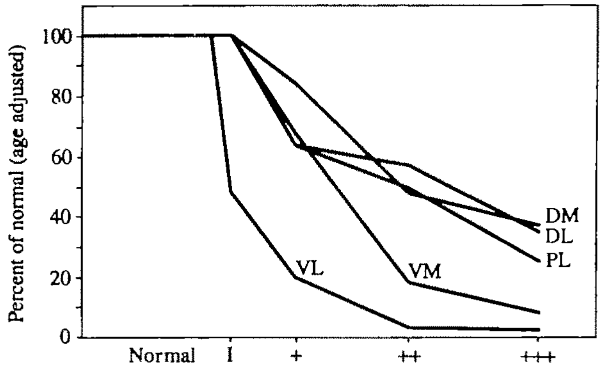

FIG 8 *Topographical progression of Parkinson's disease* Horizontal axis phase of disease from no neuronal loss (normal) through presymptomatic disease (I: incidental Lewy body cases) to mild (+), moderate (++) and severe (+++) symptomatic Parkinson's disease Vertical axis: average age adjusted regional counts for each group

percent loss is shown in Fig. 5F. The difference between regions is not as distinct as occurs in PD and SND. There was no significant difference between the divisions of the ventral tier, VM, VI and VL. VM sustained greater losses than the dorsal tier divisions DM ($P < 0.05$), DL and PL ($P < 0.001$). There was no difference between the middle groups VI, VL, DM and DL. PL was relatively spared compared with all the other regions ($P < 0.02$). Compared with PD, losses in the dorsal tier were greater by 30% ($P < 0.001$). Losses in the lateral ventral tier (VI and VL combined) were smaller than in PD by 10% ($P < 0.01$) and smaller than moderate/severe PD by 17% ($P < 0.001$).

DISCUSSION

The anatomy of the substantia nigra may be crucial to the understanding of its pathology. The pars compacta is divided into a ventral and dorsal tier. Gerfen *et al.* (1987) found that in the rat, the ventral tier projects to the striatal striosomes and the dorsal tier to the matrix. The striosomes project back to the cell bodies and proximal dendrites of the ventral tier and the matrix projects back to the pars reticulata and distal dendrites of the ventral tier. The striatal striosomes and matrix are histochemically distinct and have separate dendritic fields. The striosomal projecting nigral neurons of the cat have a high concentration of sigma receptors (Graybiel *et al.*, 1989) and the dorsal tier is marked by the presence of calcium binding protein (Gerfen *et al.*, 1985). Also there are developmental differences, the ventral tier forms connections with the striatum before the dorsal tier (Olson *et al.*, 1972). In PD, the ventral tier and especially its lateral part bears the brunt of neuronal loss, which suggests that the cellular characteristics or connections of the ventral tier may be important in providing clues to the pathogenesis of PD.

Each tier of the pars compacta has several neuronal groups. In the monkey, Parent *et al.* (1983) demonstrated alternating clusters of putamen and caudate projecting neurons forming columns through the nigra. It is possible that the anatomical groupings seen in the human correspond to these clusters and that there may be associated functional divisions.

Topographical studies of the nigrostriatal projection in the monkey have established that the oral nigra projects mainly to the head of the caudate and the caudal nigra projects to the putamen and the body of the caudate (Carpenter and Peter, 1972; Szabo, 1980). The lateral ventral nigra projects to the dorsal putamen. In PD, neuronal loss begins in the lateral ventral tier and throughout the illness this remains the region most severely affected. Kish *et al.* (1988) in a post-mortem study of PD found severe dopamine depletion in the putamen with relative sparing of the caudate. Within the putamen, the dorsal and intermediate zones were more depleted than the ventral, but severe dopamine reduction occurred in all regions.

The correlation between the regional selectivity of PD and its clinical expression is uncertain. The putamen is considered to be predominantly involved in motor programming and the caudate in cognition (DeLong *et al.*, 1983). The motor cortex input to the putamen is somatotopically organized. The leg area of the motor cortex projects to the dorsal zone of the putamen in non-human primates, the arm area to the intermediate zone and the head area to the ventral zone (Künzle, 1975). In PD, cell loss starting in the lateral ventral nigra suggests that dopamine depletion starts in the dorsal putamen. If striatal function mirrors the motor cortex input then symptoms would be expected to start in the leg. However, it is more common for symptoms to start in the arm (Schelosky and Poewe, 1990). It can be argued that a small deficit of hand function is soon noted by the patient, but the same deficit in the leg goes unnoticed. Furthermore, the bipedal gait of the human may explain the difference. In contrast, dystonia in young onset PD usually begins in the leg and often does not involve the arm.

In the past ageing has been considered to play an important role in the pathogenesis of PD, because of the considerable neuronal loss with advancing age in the substantia nigra. This study confirmed a linear fallout of pigmented neurons at a rate of 4.7% per decade in the caudal pars compacta.

In the biphasic theory of ageing and PD, the rate of neuronal loss in the second phase including the period of symptomatic PD is equivalent to the rate of neuronal loss seen in normal ageing. However, the rate of loss in cases of established PD is not linear but exponential and in the first decade there is a 45% loss, 10 times greater than is seen in normal ageing. McGeer *et al.* (1988) have also found that the rate of neuronal loss in PD is greater than could be accounted for by ageing by estimating the numbers of degenerating neurons at the time of death.

The alternative notion of PD being a form of accelerated ageing also seems improbable. Neuronal loss due to ageing shows marked regional variation in the nigra. Losses are greatest in the dorsal tier (6.9% per decade) followed by the medial ventral tier (5.4%) and least in the lateral ventral tier (2.1%). If PD is due to an acceleration of normal ageing then the pattern of cell loss should be similar to that seen as a result of normal ageing. In fact, the complete opposite applies. Neuronal loss in PD is greatest in the lateral ventral tier (average loss 91% excluding ageing) followed by the medial ventral tier (71%) and the dorsal tier (56%). These findings are inconsistent with the accelerated ageing theory.

It seems likely that PD is a relatively acute monophasic illness. The exponential loss of neurons and greater losses early in the disease means that the presymptomatic phase is considerably shorter than previously suspected, lasting around 5 yrs. At the onset of symptoms, striatal dopamine is reduced by 80%, but the total caudal nigral count is only reduced by about 50% (lateral ventral tier by 70%). This suggests that the remaining neurons are dysfunctioning and Hirsch *et al.* (1988) have found that 17% of pigmented nigral neurons in PD failed to stain for tyrosine hydroxylase.

It has been proposed that the presymptomatic phase of PD is represented by incidental Lewy body cases, which exhibit neuronal loss intermediate between control and PD cases (Forno, 1969). Hansen *et al.* (1990) have recently challenged this concept by suggesting that Lewy bodies may be a feature of normal ageing. They found in a study of 13 patients with dementia and Lewy bodies at autopsy that 4 had no cell loss in the nigra. However, this report was not supported by any quantitative evidence and no regional morphometry was carried out. In this study of 7 incidental cases, there was an average 27% loss of nigral neurons in excess of ageing ($P < 0.01$). Regionally, this loss was confined to the lateral ventral tier with an average loss of 52% ($P < 0.001$) similar to the pattern of cell loss seen in PD. This suggests that incidental Lewy bodies are indicative of presymptomatic PD rather than a feature of normal ageing. Furthermore in PD, neuronal loss appears to be confined to the lateral ventral tier early in the disease, but by the time symptoms appear it has spread to the other regions and in particular the medial ventral tier.

There is a discrepancy between the prevalence of incidental Lewy body cases and the prevalence of clinical PD in the community. This could be explained by a long presymptomatic phase with the majority of incidental cases dying before the onset of parkinsonism (Gibb and Lees, 1988). However, if there is indeed as our results suggest a relatively short presymptomatic phase this explanation is untenable. It might be that PD is considerably under-diagnosed in the elderly. The incidence of new PD cases has been reported to fall after the age of 75 (Schoenberg, 1986). Two of the 7 incidental Lewy body cases in this study might have had undiagnosed PD with an onset of parkinsonism at the age of 78 yrs. Therefore, the difference between the prevalence of PD and incidental cases might be spurious, because of an underestimation of PD in the elderly and a consequent overestimation of the number of true incidental Lewy body cases.

PD regional nigral selectivity is relatively specific when compared with SND and SRO. Both PD and SND share a predilection for the lateral ventral tier, which is not seen in SRO. Differences were seen in the involvement of the dorsal tier, which was greatest in SRO followed by SND and least in PD. Neuronal loss in the dorsal tier was greater in SND and SRO than in PD by approximately 21% and 30%, respectively. In the monkey, Parent *et al.* (1983) found that putaminal projecting clusters were more frequent in the caudal ventral nigra and that caudate clusters were more frequent in the oral dorsal nigra probably corresponding to the ventral and dorsal tiers, respectively. This would suggest that greater involvement of the dorsal tier would result in greater reduction of nigral terminals in the caudate. This would explain the differences in ^{18}F-dopa striatal uptake between PD, SND and SRO on positron emission tomography (Brooks *et al.*, 1990). Reduction of uptake in the caudate was greatest in SRO followed by SND and least in PD.

Since the advent of MPTP induced parkinsonism it has been mooted that PD is due to one or several environmental neurotoxins (Davis *et al.*, 1978). However, epidemiological studies have failed to unearth any single conclusive exogenous factor although some association with exposure to herbicides and residence in rural areas has been implicated (Barbeau *et al.*, 1986). Furthermore, despite close similarity between the MPTP lesion and that seen in PD, differences in the pathological lesion exist. Although the nigral lesion has a ventral predilection (German *et al.*, 1988), the caudate and putamen are equally depleted of dopamine, unlike PD in which there is some sparing of the caudate (Pifl *et al.*, 1988). There is also some question that MPTP in the human spares the nucleus basalis of Meynert and that Lewy bodies do not occur (Burns *et al.*, 1984). However, it is possible that some of these histological differences are due to the acute administration of the toxin.

Neuromelanin has been implicated in the pathogenesis of PD (Hirsch *et al.*, 1988), but non-pigmented regions can be equally affected (Marsden, 1983). It has been speculated that because MPP$^+$ has a high affinity for neuromelanin it may be slowly released after the initial exposure and result in chronic toxicity (D'Amato *et al.*, 1986). However, we found that the neuromelanin-containing cells with the least pigment to be the most affected in PD suggesting that neuromelanin accumulation is not a pathogenetic factor (Gibb *et al.*, 1990). However, neuromelanin may be important in the pathogenesis of age-related neuronal attrition as ageing seems to be confined to the most heavily pigmented regions. It is known that the formation of neuromelanin is associated with the generation of free radicals and toxic quinones (Graham, 1978), which may be responsible for age-related cell death.

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REFERENCES

ANDREWS JM, TERRY RD, SPATARO J (1970) Striatonigral degeneration. Clinical-pathological correlations and response to stereotaxic surgery. *Archives of Neurology,* **23,** 319–329.

ANZIL AP (1969) Progressive supranuclear palsy: case report with pathological findings. *Acta Neuropathologica, Berlin,* **14,** 72–76.

BANNISTER R, GIBSON W, MICHAELS L, OPPENHEIMER DR (1981) Laryngeal abductor paralysis in multiple system atrophy: a report on three necropsied cases, with observations on the laryngeal muscles and the nuclei ambigui. *Brain,* **104,** 351–368.

BARBEAU A (1984) Etiology of Parkinson's disease: a research strategy. *Canadian Journal of Neurological Sciences,* **11,** 24–28.

BARBEAU A, ROY M, CLOUTIER T, PLASSE L, PARIS S (1986) Environmental and genetic factors in the etiology of Parkinson's disease. *Advances in Neurology,* **45,** 299–306.

BORIT A, RUBINSTEIN LJ, URICH H (1975) The striatonigral degenerations: putaminal pigments and nosology. *Brain,* **98,** 101–112

BROOKS DJ, IBANEZ V, SAWLE GV, QUINN N, LEES AJ, MATHIAS CJ *et al.* (1990) Differing patterns of striatal ^{18}F-dopa uptake in Parkinson's disease, multiple system atrophy, and progressive supranuclear palsy. *Annals of Neurology,* **28,** 547–555.

BUONANNO F, NARDELLI E, ONNIS L, RIZZUTO N (1975) Striato-nigral degeneration: report of a case with an unusually short course and multiple system degenerations. *Journal of the Neurological Sciences,* **26,** 545–553.

BURNS RS, MARKEY SP, PHILLIPS JM, CHIUEH CC (1984) The neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in the monkey and man. *Canadian Journal of Neurological Sciences,* **11,** 166–168.

CALNE DB, LANGSTON JW, MARTIN WRW, STOESSL AJ, RUTH TJ, ADAM MJ *et al.* (1985) Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. *Nature, London,* **317,** 246–248.

CALNE DB, EISEN A, MCGEER E, SPENCER P (1986) Alzheimer's disease, Parkinson's disease, and motoneurone disease: abiotropic interaction between ageing and environment? *Lancet,* **ii,** 1067–1070

CARLSSON A, NYBERG P, WINBALD B (1984) The influence of age and other factors on concentrations of monoamines in the human brain. In: *Brain Monoamines in Normal Aging and Dementia.* Edited by P. Nyberg. Sweden: Umea Medical Dissertations, pp. 53–84.

CARPENTER MB, PETER P (1972) Nigrostriatal and nigrothalamic fibers in the rhesus monkey *Journal of Comparative Neurology,* **144,** 93–115.

D'AMATO RJ, LIPMAN ZP, SNYDER SH (1986) Selectivity of the parkinsonian neurotoxin MPTP: toxic metabolite MPP$^+$ binds to neuromelanin. *Science,* **231,** 987–989.

DAVIS GC, WILLIAMS AC, MARKEY SP, EBERT MH, CAINE ED, REICHERT CM *et al.* (1979) Chronic parkinsonism secondary to intravenous injection of meperidine analogues. *Psychiatry Research,* **1,** 249–254.

DELONG MR, GEORGOPOULOS AP, CRUTCHER MD (1983) Cortico-basal ganglia relations and coding of motor performance. *Experimental Brain Research,* Supplement 7, 30–40.

DUVOISIN RC, YAHR MD (1965) Encephalitis and parkinsonism. *Archives of Neurology, Chicago,* **12,** 227–239

Evarts EV, Teravàinen HT, Beuchert DE, Calne DB (1979) Pathophysiology of motor performance in Parkinson's disease. In: *Dopaminergic Ergot Derivatives and Motor Function.* Edited by K Fuxe and D. B. Calne. Oxford: Pergamon Press, pp. 45–59.

Evarts EV, Teravàinen H, Calne DB (1981) Reaction time in Parkinson's disease. *Brain,* **104,** 167–186.

·orno LS (1969) Concentric hyalin intraneuronal inclusions of Lewy type in the brains of elderly persons (50 incidental cases): relationship to parkinsonism. *Journal of the American Geriatrics Society,* **17,** 557–575.

Gerfen CR, Baimbridge KG, Miller JJ (1985) The neostriatal mosaic: compartmental distribution of calcium-binding protein and parvalbumin in the basal ganglia of the rat and monkey. *Proceedings of the National Academy of Sciences of the USA,* **82,** 8780–8784.

Gerfen CR, Herkenham M, Thibault J (1987) The neostriatal mosaic: II. Patch- and matrix-directed mesostriatal dopaminergic and non-dopaminergic systems. *Journal of Neuroscience,* **7,** 3915–3934.

German DC, Dubach M, Askari S, Speciale SG, Bowden DM (1988) 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonian syndrome in *Macaca fascicularis*: which midbrain dopaminergic neurons are lost? *Neuroscience,* **24,** 161–174.

Gibb WRG, Lees AJ (1988) The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry,* **51,** 745–752.

Gibb WRG, Fearnley JM, Lees AJ (1990) The anatomy and pigmentation of the human substantia nigra in relation to selective neuronal vulnerability. *Advances in Neurology,* **53,** 31–34.

Graham DG (1978) Oxidative pathways for catecholamines in the genesis of neuromelanin and cytotoxic quinones. *Molecular Pharmacology,* **14,** 633–643.

Graybiel AM, Besson M-J, Weber E (1989) Neuroleptic-sensitive binding sites in the nigrostriatal system: evidence for differential distribution of sigma sites in the substantia nigra, pars compacta of the cat *Journal of Neuroscience,* **9,** 326–338.

Hansen L, Salmon D, Galasko D, Masliah E, Katzman R, DeTeresa R *et al.* (1990) The Lewy body variant of Alzheimer's disease. a clinical and pathological entity. *Neurology, Cleveland,* **40,** 1–8.

Hassler R (1937) Zur Normalanatomie der Substantia nigra. Versuch einer architektonischen Gliederung. *Journal für Psychologie und Neurologie,* **48,** 1–55.

Hassler R (1938) Zur Pathologie der Paralysis agitans und des postenzephalitischen Parkinsonismus *Journal für Psychologie und Neurologie,* **48,** 387–476.

Hirai S (1968) Histochemical study on the regressive degeneration of the senile brain, with special reference to the aging of the substantia nigra. *Advances in Neurological Science, Tokyo,* **12,** 848–849 (in Japanese).

Hirsch E, Graybiel AM, Agid YA (1988) Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature, London,* **334,** 345–348.

Hodge CF (1894) Changes in ganglion cells from birth to senile death Observations on man and honey-bee. *Journal of Physiology, London,* **17,** 129–134.

Hoehn MM, Yahr MD (1967) Parkinsonism. onset progression, and mortality. *Neurology, Minneapolis,* **17,** 427–442.

Jellinger K, Danielczyk W (1968) 'Striato-nigrale degeneration'. *Acta Neuropathologica, Berlin,* **10,** 242–257.

Jellinger K (1971) Progressive supranuclear palsy (subcortical argyrophilic dystrophy). *Acta Neuropathologica, Berlin,* **19,** 347–352.

Kish SJ, Shannak K, Hornykiewicz O (1988) Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease: pathophysiologic and clinical implications. *New England Journal of Medicine,* **318,** 876–880.

Künzle H (1975) Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis. Brain Research, Amsterdam,* **88,** 195–209.

McGeer PL, McGeer EG, Suzuki JS (1977) Aging and extrapyramidal function. *Archives of Neurology, Chicago,* **34,** 33–35.

McGeer PL, Itagaki S, Akiyama H, McGeer EG (1988) Rate of cell death in parkinsonism indicates active neuropathological process. *Annals of Neurology,* **24,** 574–576.

Mann DMA, Yates PO (1983) Possible role of neuromelanin in the pathogenesis of Parkinson's disease. *Mechanisms of Ageing and Development,* **21,** 193–203.

Mann DMA, Yates PO, Marcyniuk B (1984) Monoaminergic neurotransmitter systems in presenile Alzheimer's disease and in senile dementia of Alzheimer type. *Clinical Neuropathology*, **3**, 199–205.

Marsden CD (1983) Neuromelanin and Parkinson's disease. *Journal of Neural Transmission*, **19**, Supplement, 121–141.

Marsden CD (1990) Parkinson's disease. *Lancet*, **335**, 948–952.

Mattock C, Marmot M, Stern G (1988) Could Parkinson's disease follow intra-uterine influenza?: a speculative hypothesis. *Journal of Neurology, Neurosurgery, and Psychiatry*, **51**, 753–756.

Olson L, Seiger Å, Fuxe K (1972) Heterogeneity of striatal and limbic dopamine innervation: highly fluorescent islands in developing and adult rats. *Brain Research, Amsterdam*, **44**, 283–288.

Olszewski J, Baxter D (1954) *Cytoarchitecture of the Human Brain Stem.* Basel: S. Karger, pp. 131–132.

Parent A, Mackey A, De Bellefeuille L (1983) The subcortical afferents to caudate nucleus and putamen in primate: a fluorescence retrograde double labeling study. *Neuroscience*, **10**, 1137–1150.

Pifl C, Schingnitz G, Hornykiewicz O (1988) The neurotoxin MPTP does not reproduce in the rhesus monkey the interregional pattern of striatal dopamine loss typical of human idiopathic Parkinson's disease. *Neuroscience Letters*, **92**, 228–233.

Rajput AH, Kazi KH, Rozdilsky B (1972) Striatonigral degeneration response to levodopa therapy. *Journal of the Neurological Sciences*, **16**, 331–341.

Riederer P, Wuketich S (1976) Time course of nigrostriatal degeneration in Parkinson's disease. A detailed study of influential factors in human brain amine analysis. *Journal of Neural Transmission*, **38**, 277–301.

Schelosky L, Poewe W (1990) Topographical onset and progression of motor symptoms in idiopathic Parkinson's disease. *Movement Disorders*, **5**, Supplement 1, 13.

Scherman D, Desnos C, Darchen F, Pollak P, Javoy-Agid F, Agid Y (1989) Striatal dopamine deficiency in Parkinson's disease: role of aging *Annals of Neurology*, **26**, 551–557.

Schoenberg BS (1986) Descriptive epidemiology of Parkinson's disease: disease distribution and hypothesis formulation. *Advances in Neurology*, **45**, 277–284.

Sharpe JA, Rewcastle NB, Lloyd KG, Hornykiewicz O, Hill M, Tasker RR (1973) Striatonigral degeneration: response to levodopa therapy with pathological and neurochemical correlation. *Journal of the Neurological Sciences*, **19**, 275–286.

Steele JC, Richardson JC, Olszewski J (1964) Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia and dementia. *Archives of Neurology, Chicago*, **10**, 333–359.

Sung JH, Mastri AR, Segal E (1979) Pathology of Shy-Drager syndrome. *Journal of Neuropathology and Experimental Neurology*, **38**, 353–368.

Szabo J (1980) Organization of the ascending striatal afferents in monkeys. *Journal of Comparative Neurology*, **189**, 307–321.

Takei Y, Mirra SS (1973) Striatonigral degeneration: a form of multiple system atrophy with clinical parkinsonism. In: *Progress in Neuropathology*, Volume II. Edited by H. M. Zimmerman. New York and London: Grune and Stratton, pp. 217–251.

Tatton WG, Lee RG (1975) Evidence for abnormal long-loop reflexes in rigid parkinsonian patients. *Brain Research, Amsterdam*, **100**, 671–676.

Teräväinen H, Calne DB (1983) Motor system in normal aging and Parkinson's disease. In: *The Neurology of Aging*. Edited by R. Katzman and R. Terry. Philadelphia: F A. Davis, pp. 85–109.

Trotter JL (1973) Striatonigral degeneration, Alzheimer's disease, and inflammatory changes. *Neurology, Minneapolis*, **23**, 1211–1216.

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MYOTONIC DYSTROPHY

PREDICTIVE VALUE OF NORMAL RESULTS ON CLINICAL EXAMINATION

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SUMMARY

Myotonic dystrophy (DM) is well known for its highly variable clinical picture, including the age at which symptoms are first detected. In order to assess the proportion of asymptomatic gene carriers at different ages, we have used linked DNA markers to study individuals at 50% genetic risk of DM, in whom neurological examination, slit-lamp examination and electromyography (EMG) had failed to show diagnostic signs. A total of 139 asymptomatic offspring of DM patients were studied. Our analyses identified 11 out of these 139 as probable gene carriers. Our data show that penetrance of the DM gene increases with age. After correction for the possibility of genetic recombination between the DM gene and the DNA markers used, we calculated the residual chance of carrying the DM gene as 8.3% for clinically normal offspring aged between 20 and 39 yrs.

We evaluated several factors that might influence this figure. Neither the sex of the propositus nor that of the affected parent modified the risk of carrying the DM gene. Presence of aspecific lens opacities also did not correlate with the risk of having inherited the DM gene. Since a significant proportion of DM gene carriers are not detected by neurological examination, including slit-lamp examination and EMG, these results confirm the need for DNA analysis in asymptomatic offspring of DM patients.

INTRODUCTION

Myotonic dystrophy (DM) is an autosomal dominant multisystem disorder with variable expressivity and incomplete penetrance. A number of studies have documented that the proportion of symptomatic patients increases with age, the median age at onset of symptoms being 20–25 yrs (Harper, 1989). EMG studies and slit-lamp examination are useful for the detection of subclinically affected individuals (Polgar *et al.*, 1972). It has been suggested that the use of these ancillary investigations will allow the detection of most, if not all, gene carriers either by young adulthood (Harper, 1973, 1989), or by age 40 (Bundey, 1974). Nevertheless, it is likely that occasional gene carriers remain undetected. This is supported by reports of obligate gene carriers who failed to show

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diagnostic abnormalities at an advanced age (Höweler, 1986; Streib *et al.*, 1987; personal observations).

The assignment of the DM gene to chromosome 19, and the subsequent development of closely linked genetic markers have created the possibility of using DNA linkage analysis for predictive testing in DM families. We here report the use of DNA analysis to assess the predictive value of a full clinical evaluation, including EMG and slit-lamp examination in a large cohort of individuals at 50% risk of developing DM.

MATERIAL AND METHODS

Clinical data

We have used data from a previous linkage study (Brunner *et al.*, 1989*b*) and from the current diagnostic DNA service at our department to examine the value of a negative clinical examination in persons at risk for DM. We examined the DNA data for all individuals who fulfilled the following criteria: (1) prior risk of DM 50%; (2) absence of clinical or electrical myotonia, significant muscle weakness, multicoloured lens opacities or congenital myotonic dystrophy.

In all cases, age given corresponds to the age at clinical examination. If clinical examination had been performed at different ages, only the age at first examination was used.

With rare exceptions, individuals in our study had been examined clinically at one of the 8 Dutch university hospitals.

DNA data

DNA analysis was performed using previously described methods (Brunner *et al.*, 1989*a*, 1989*b*; Smeets *et al.*, 1989, 1991). Closely linked markers that were used defined the following loci: BCL3, APOC1, APOC2, CKM, ERCC1, D19S63, D19S112, D19S51, D19S50, KLK and RRAS.

Recombination frequencies used in risk calculations were as published elsewhere (LeBeau *et al.*, 1988; Korneluk *et al.*, 1989*a*; Johnson *et al.*, 1990), with the following modifications: for APOC2 and APOC1, recombination frequencies were taken as 2% and 3%, respectively; for D19S63, a recombination frequency of $\leq 1\%$ was used, based on our own data as well as on data from other laboratories. [So far, no recombination has been observed between the DM gene and this locus (Brook *et al.*, 1991)]; for D19S112, we used an estimated recombination frequency of 2% (H. Smeets, unpublished data); for both KLK and RRAS, we assumed a recombination frequency of 12%, based on map position and two-point linkage analysis (Smeets *et al*, 1991; and unpublished data).

Linkage phase (i.e. the marker allele with which the DM gene segregates within a particular family) was always established through examination of affected individuals in accordance with published criteria (Griggs *et al.*, 1989).

Statistical evaluation

In order to calculate the chance of a false negative diagnosis on clinical examination, we derived the following formulas.

(1) *Notations*

DM^+	Myotonic Dystrophy gene present
DM^-	Myotonic Dystrophy gene absent
DNA^-	Low risk marker allele
DNA^+	High risk marker allele
$CLIN^-$	Clinical examination negative
$CLIN^+$	Clinical examination positive

(2) *Assumptions*

(*a*) The prior risk of DM equals 50% for all individuals in the study.

$P\,[DM^+] = 0.5.$

(*b*) Using linked DNA markers, the chances of a false positive and of a false negative diagnosis are symmetric and known.

$P\ [\text{DNA}^-|\text{DM}^+] = P\ [\text{DNA}^+|\text{DM}^-] = q.$

(*c*) DNA diagnosis and clinical diagnosis are conditionally independent.

$P\ [\text{DNA}^+,\text{CLIN}^+|\text{DM}^+] = P\ [\text{DNA}^+|\text{DM}^+] \times P\ [\text{CLIN}^+|\text{DM}^+].$

(*d*) The specificity of a positive clinical diagnosis of DM is 1.

$P\ [\text{CLIN}^-|\text{DM}^-] = 1.$

(*e*) Call $p = P\ [\text{CLIN}^+|\text{DM}^+]$ (the sensitivity of the clinical examination) the unknown parameter.

(3) *Formula*

Using simple probability rules:

$$P\ [\text{DNA}^-|\text{CLIN}^-] = \frac{P\ [\text{DNA}^-,\text{CLIN}^-]}{P\ [\text{CLIN}^-]}$$

$$= \frac{P\ [\text{DNA}^-,\text{CLIN}^-|\text{DM}^+] \times P\ [\text{DM}^+] + P\ [\text{DNA}^-,\text{CLIN}^-|\text{DM}^-] \times P\ [\text{DM}^-]}{P\ [\text{CLIN}^-|\text{DM}^+] \times P\ [\text{DM}^+] + P\ [\text{CLIN}^-|\text{DM}^-] \times P\ [\text{DM}^-]}$$

$$= \frac{q\ (1-p)\ ½ + (1-q)\ ½}{(1-p)\ ½ + ½} = \frac{q-qp+1-q}{1-p+1} = \frac{1-qp}{2-p}$$

(4) *Estimation of sensitivity and negative predictive value*

We estimated p from the equation:

$$\frac{1-qp}{2-p} = \text{sample fraction DNA}^- = \frac{n-d}{n}$$

Where: d = number of individuals with a high risk marker genotype; n = number of clinically normal individuals tested with DNA markers

Also: $\frac{1}{2-p}$ is the negative predictive value of the clinical examination.

Using Taylor series expansion an approximation of the standard error can be calculated (Mood *et al.*, 1974).

Assumption (*a*) is correct because DM shows regular autosomal dominant inheritance, and only offspring of known gene carriers were included in this study

Assumption (*b*) and (*c*) are met, because genetic recombination frequency is not dependent on clinical expression of the DM gene.

Assumption (*d*) is met if strict diagnostic criteria are used (Griggs *et al.*, 1989)

All comparisons were performed by χ^2-test.

RESULTS

A total of 151 fully investigated, clinically normal individuals were tested, using the DNA marker systems shown in Table 1. A recombination event in the vicinity of the DM gene precluded accurate phase determination in 1 nuclear family. This family was excluded from subsequent analyses. Other reasons for exclusion were: non-paternity shown by DNA analysis (4 individuals in 2 families), and non-informativity of the DNA analysis, defined as >5% chance of incorrect genotype assignment (6 individuals in 5 families). The final analysis included 139 individuals (66 males and 73 females) in 69 families. All individuals were at 50% prior risk of DM. None had unequivocal clinical

TABLE 1 MARKERS USED FOR DNA DIAGNOSIS

Probe name/ method	*Locus*	*Location relative to DM*	*Recombination fraction*	*Reference*
pα1.4P	BCL3	Proximal	4%	Korneluk *et al.* (1989*a*)
PCR-assay	APOC1	Proximal	3%	Nillesen *et al.* (1990)
VSSM	APOC2	Proximal	2%	LeBeau *et al.* (1988), Smeets *et al.* (1989)
pSC11	APOC2	Proximal	2%	LeBeau *et al* (1988)
pE15	APOC2	Proximal	2%	LeBeau *et al.* (1988)
pCKMM3′	CKM	Proximal	1%	LeBeau *et al.* (1988)
VSSM	ERCC1	Proximal	1%	LeBeau *et al* (1988); Smeets *et al.* (1991)
pE0.8	ERCC1	Proximal	1%	LeBeau *et al.* (1988); Shutler *et al.* (1991)
pD10	D19S63	Unknown	≤1%	Brook *et al.* (1991)
pX75b	D19S112	Distal	2%	Unpublished data
p134c	D19S51	Distal	2½%	Johnson *et al.* (1990)
pEWRB1 1	D19S50	Distal	9%	Korneluk *et al.* (1989*b*); LeBeau *et al.* (1988)
pEWRB1 4	D19S50	Distal	9%	Korneluk *et al* (1989*b*), LeBeau *et al* (1988)
pHGK	KLK	Distal	12%	Hermens *et al* (1990); Smeets *et al* (1991)
VSSM	RRAS	Distal	12%	Smeets *et al.* (1991)

*All probes detect conventional restriction fragment length polymorphisms (RFLPs), except: VSSM = variable simple sequence motifs; PCR = polymerase chain reaction

or electrical myotonia, specific multicoloured lens opacities, significant muscle wasting or weakness, or signs of congenital myotonic dystrophy. DNA analysis was usually informative for either the CKM, ERCC1 or D19S63 locus. On average, the diagnostic reliability of the DNA analysis was 98.44% (range 96% to >99%). In 11 individuals, DNA analysis indicated a high probability (mean 98.82%; range 98% to >99%) of carrying the DM gene (Table 2). The number of expected false positive diagnoses due to genetic recombination in our sample equals only 2.16 (139×0.0156). Therefore, approximately 9 (= 11−2.16) individuals tested should be asymptomatic gene carriers.

Using the equations given in the Material and Methods section, we calculated the negative predictive value (i.e. the probability of not carrying the DM gene for a person

TABLE 2 RESULTS OF DNA ANALYSIS IN 139 CLINICALLY NORMAL OFFSPRING OF PATIENTS WITH DM

	DNA analysis	
Age	*Low risk genotype**	*High risk genotype**
0–9	3	0
10–19	12	2
20–29	60	4
30–39	25	5
40–49	11	0
50–59	12	0
60–69	5	0
Total	128	11

*High and low risk genotypes were defined as a >95% and a <5% chance of carrying the DM gene, respectively with a prior risk of 50% and a negative clinical diagnosis). For the complete study, this was 93.4% (SD ±2.5%). In order to derive estimates that can be used for genetic counselling purposes, we then calculated the negative predictive value for persons <20 yrs, between 20 and 39 yrs, and >40 yrs of age. In these age groups, the negative predictive value was calculated as 89.4% (SD ± 8.9%), 91.7% (SD ± 3.5%) and 99.8% (SD ± 2.6%), respectively. We also considered the possibility that other factors, such as sex of the propositus or of the affected parent, might influence the penetrance of the DM gene. Moreover, we compared individuals with high and low risk genotypes with regard to the presence of non-diagnostic signs, such as atypical cataract or mild muscular weakness without myotonia. As can be seen in Tables 3 and 4, these parameters were equally distributed among persons with and without the DM gene.

TABLE 3 DISTRIBUTION OF HIGH AND LOW RISK GENOTYPES ACCORDING TO OTHER VARIABLES THAT WERE ANALYSED

	Low risk genotype (n = 128)*	*High risk genotype* (n = 11)*	*P-value by χ^2-test*
Propositus male/female	59/69	7/4	0 42
Mother/father affected	51/77	5/6	0.96
Non-specific features present/absent	24/104	3/8	0 77

*High and low risk genotypes were defined as a >95% and a <5% chance of carrying the DM gene, respectively.

TABLE 4. FEATURES THAT WERE CONSIDERED SUGGESTIVE BUT NOT DIAGNOSTIC OF DM

	Low risk genotype (n = 128)*	*High risk genotype* (n = 11)*
Non-specific lenticular opacities	14	2
Ptosis	1	1
Mild muscular weakness	2	0
Equivocal clinical myotonia/normal EMG	4	1
ECG abnormalities[+]	2	0
Mental retardation	1	1
EMG abnormalities other than myotonia	1	0
Total present	24[a]	3[b]
Absent	104	8

*High and low risk genotypes were defined as a >95% and a <5% chance of carrying the DM gene, respectively. [+] ECG abnormalities were not searched for systematically. [a] One individual with both aspecific lens abnormalities and equivocal clinical myotonia. [b] One individual with both aspecific lens abnormalities and ptosis and one individual with both aspecific lens abnormalities and equivocal clinical myotonia.

In order to validate further our results, we tried to obtain updated clinical data for patients with a high risk DNA genotype. Additional data were collected for 5 of the 11 individuals that had been indicated by DNA marker studies as putative carriers of the DM gene.

A 39-yr-old male was found to carry the high risk allele for the flanking markers APOC2 and for D19S51. Upon clinical examination, EMG and slit-lamp examination he was completely normal. Four years later, he is still completely asymptomatic. However, one of his sons now shows action and percussion myotonia and muscular weakness, thereby identifying him as an obligate gene carrier.

EMG examination was repeated in 4 asymptomatic individuals identified as probable DM gene carriers by DNA analysis. In 2 females, EMG and slit-lamp examination remained negative at ages 27 and 37 yrs respectively, 3 yrs after first examination. In another female, EMG showed electrical myotonia at age 41 yrs, 5 yrs after the first examination had been negative. In a male, clinical examination, including EMG was normal at age 33 and 35 yrs. However, another EMG at age 37 yrs showed unequivocal myotonia.

Follow-up data have thus confirmed the presence of the DM gene in 3 of 5 individuals with a high risk genotype.

DISCUSSION

Previous studies of penetrance in DM have relied largely on the age at which the expected 50% ratio of affected individuals was reached. These studies have suggested that most (if not all) DM gene carriers should be detectable by young adulthood (Harper, 1973, 1989) or by age 40 (Bundey, 1974). However, not all relatives were studied, and EMG studies were performed in only a minority of patients. Therefore, estimates of penetrance from these studies were necessarily imprecise. Another similar study (Schubert *et al.*, 1980) is difficult to interpret, since probands may have been included in the analysis (Bundey, 1982). Published curves of age at onset (Harper, 1989) refer to self-reported symptoms, and therefore lead to overestimation of the age at which the disorder becomes recognizable by clinical examination.

All individuals in the study reported here had been previously examined clinically by an experienced neurologist and ophthalmologist for signs of myotonic dystrophy. It is possible that a higher percentage of gene carriers might have been detected if all individuals had been investigated by a single investigator, including standardized EMG of muscles such as the orbicularis oris and masseter (Streib and Sun, 1983). Nonetheless, we feel that our data give a realistic estimate of the diagnostic accuracy that is attained in tertiary care university hospitals. This is supported by the fact that individuals with a high risk genotype appeared evenly distributed among the referring centres.

Overall sensitivity of the clinical assessment was 93% in our sample (Table 5). Diagnostic accuracy increased with age. Since the number of individuals less than 20 yrs is relatively small, the estimated negative predictive value for this age group (89.4% ±8.9) is very tentative with wide confidence limits. Others have noted that a significant proportion of young DM gene carriers may be missed by clinical examination (including EMG and slit-lamp examination), especially before 10 yrs of age (Harper, 1973). However, in sibships in which an older sibling has congenital myotonic dystrophy, early detection may be less difficult (Bundey, 1974; O'Brien *et al.*, 1983). No sibs of congenitally affected individuals were studied here. Between the ages of 20 and 39 yrs, the negative predictive value of a normal clinical examination was 91.7% (±3.5%) (Table 5). This figure is of particular importance, since genetic counselling is most often requested by individuals in this age group. Of 28 individuals aged 40 yrs or older, none had a high risk genotype. It is likely that fewer cases are missed over the age of 40 yrs than under the age of 40 ($P = 0.08$), but more data are needed to derive an accurate estimate of penetrance in the older age groups.

The excess of affected fathers in our series (Table 3) is largely due to individuals older than 40 yrs. For this age group, the father was affected in 21 out of 27 individuals tested. An excess of paternal transmission of DM was found in another recent study (Veillette *et al.*, 1989). As suggested by others (Harper, 1989), this may reflect a tendency for milder involvement in the offspring of affected males, thus bringing their families to medical attention at a relatively advanced age. This phenomenon is the reverse of the well-known overrepresentation of maternal transmission among cases of congenital myotonic dystrophy. In spite of these influences of parental sex on gene expression in DM, we found no differences in the proportion of high risk genotypes in the offspring of male and female DM patients (6/83 and 5/56, $P > 0.10$). Sex of the propositus also had no apparent effect, 4/73 females and 7/66 males being identified as probable DM gene carriers ($P > 0.10$).

In a study, reporting on diagnostic DNA analysis in DM, Norman *et al.* (1989) found that 4 out of 34 at-risk individuals carried a high risk genotype, as determined by studies with linked DNA markers. Although their results appear similar to ours (11 out of 139 positive by DNA analysis), more detailed comparison with that study is not possible, since clinical tests, age at diagnosis, prior risk, and sex of patients and affected parents were not specified.

TABLE 5 SENSITIVITY OF CLINICAL DIAGNOSIS OF DM AND PROBABILITY THAT A CLINICALLY NORMAL INDIVIDUAL DOES NOT CARRY THE DM GENE (NEGATIVE PREDICTIVE VALUE)

Age (yrs)	*Number of individuals tested (n)*	*Number with high risk genotype (d)*	*Sensitivity of clinical diagnosis (p) (%)*	*Negative predictive value [1/(2−p)] (%)*
0–19	17	2	88.2±10.0	89.4±8.9
20–39	94	9	91.0±3.8	91.7±3.5
40–69	28	0	99.8±2.6	99.8±2.6
All ages	139	11	93.0±2.7	93.4±2.5

Some studies have emphasized the significance of additional symptoms that are compatible with a diagnosis of DM, but not specific for this disorder (e.g. Pryse-Phillips *et al.*, 1982). Our data suggest that the significance of such a 'partial syndrome' is limited, since the frequency of non-specific abnormalities was similar for those with a positive and a negative diagnosis of DM by DNA studies (3/11 and 24/128, respectively, $P > 0.10$, *see* Tables 3 and 4). The same conclusion was reached in a recent study, which reported follow-up on 44 patients with non-specific features of DM. After an average period of 2.4 yrs, 30 still showed only non-specific signs, 8 showed a typical form of DM, while 6 no longer presented any identifiable anomaly (Mathieu *et al.*, 1989).

In conclusion, our data show that for offspring of patients with DM, the risk of possessing the myotonic dystrophy gene is approximately 8% if upon complete clinical examination in young adulthood no abnormalities can be demonstrated. The likelihood of normal clinical findings in a DM gene carrier may be less after age 40 yrs, but more data are needed to confirm this. We suggest that DNA analysis should be part of the diagnostic work-up of persons at risk for myotonic dystrophy.

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REFERENCES

BROOK JD, HARLEY HG, WALSH KV, RUNDLE SA, SICILIANO MJ, HARPER PS *et al.* (1991) Identification of new DNA markers close to the myotonic dystrophy locus. *Journal of Medical Genetics*, **28**, 84–88.

BRUNNER H, COERWINKEL-DRIESSEN M, SMEETS B, SCHONK D, SCHEPENS J, OERLEMANS F *et al.* (1989*a*) Definition of subchromosomal intervals around the myotonic dystrophy locus at 19q. In: *Genetics of Neuromuscular Disorders*. Edited by C. S. Bartsocas New York: ALan R. Liss, pp. 107–114.

BRUNNER HG, SMEETS H, LAMBERMON HMM, COERWINKEL-DRIESSEN M, VAN OOST BA, WIERINGA B *et al.* (1989*b*) A multipoint linkage map around the locus for myotonic dystrophy on chromosome 19. *Genomics*, **5**, 589–595.

BUNDEY S (1974) Detection of heterozygotes for myotonic dystrophy. *Clinical Genetics*, **5**, 107–109.

BUNDEY S (1982) Myotonic dystrophy—early detection and genetic counselling. *Journal of Neurology*, **226**, 295.

GRIGGS RC, WOOD DS, THE WORKING GROUP ON THE MOLECULAR DEFECT IN MYOTONIC DYSTROPHY (1989) Criteria for establishing the validity of genetic recombination in myotonic dystrophy. *Neurology, Cleveland*, **39**, 420–421.

HARPER PS (1973) Pre-symptomatic detection and genetic counselling in myotonic dystrophy. *Clinical Genetics*, **4**, 134–140.

HARPER PS (1989) *Myotonic Dystrophy*. Second edition London: W. B. Saunders.

HERMENS R, COERWINKEL M, TRAPMAN J, RIEGMAN PHJ, VLIETSTRA RJ, SMEETS H *et al* (1990) An MspI RFLP detected by the human glandular kallikrein gene (hGK) on chromosome 19q. *Nucleic Acids Research*, **18**, 208.

HÖWELER CJ (1986) *A Clinical and Genetic Study in Myotonic Dystrophy*. Thesis, Rotterdam, pp. 66.

JOHNSON K, SHELBOURNE P, DAVIES J, BUXTON J, NIMMO E, SICILIANO MJ *et al.* (1990) A new polymorphic probe which defines the region of chromosome 19 containing the myotonic dystrophy locus. *American Journal of Human Genetics*, **46**, 1073–1081.

KORNELUK RG, MACLEOD HL, MCKEITHAN TW, BROOKS JD, MACKENZIE AE (1989*a*) A chromosome 19 clone from a translocation breakpoint shows close linkage and linkage disequilibrium with myotonic dystrophy. *Genomics*, **4**, 146–151.

KORNELUK RG, MACKENZIE AE, NAKAMURA Y, DUBÉ I, JACOB P, HUNTER AGW (1989*b*) A reordering of human chromosome 19 long-arm DNA markers and identification of markers flanking the myotonic dystrophy locus. *Genomics*, **5**, 596–604.

LEBEAU MM, PERICAK-VANCE MA (1988) Report of the committee on the genetic constitution of chromosomes 18 and 19. *Cytogenetics and Cell Genetics*, **49**, 99–101.

MATHIEU J, SIMARD M, DE BRAEKELEER M, BOILY C, DESCHÊNES A (1989) Partial syndrome of myotonic dystrophy: clinical presentation and follow-up. *Canadian Journal of Neurological Sciences*, **16**, 99–103.

MOOD AM, GRAYBILL FA, BOES DC (1974) *Introduction to the Theory of Statistics*. Third edition. Tokyo: McGraw-Hill.

NILLESEN WM, SMEETS HJM, VAN OOST BA (1990) Human ApoC1 HpaI restriction site polymorphism revealed by the polymerase chain reaction. *Nucleic Acids Research*, **18**, 3428.

NORMAN AM, FLOYD JL, MEREDITH AL, HARPER PS (1989) Presymptomatic detection and prenatal diagnosis for myotonic dystrophy by means of linked DNA markers. *Journal of Medical Genetics*, **26**, 750–754.

O'BRIEN T, NEWCOMBE RG, HARPER PS (1983) Outlook for a clinically normal child in a sibship with congenital myotonic dystrophy. *Journal of Pediatrics*, **103**, 762–763.

POLGAR JG, BRADLEY WG, UPTON ARM, ANDERSON J, HOWAT JML, PETITO F *et al.* (1972) The early detection of dystrophia myotonica. *Brain*, **95**, 761–776.

PRYSE-PHILLIPS W, JOHNSON GJ, LARSEN B (1982) Incomplete manifestations of myotonic dystrophy in a large kinship in Labrador. *Annals of Neurology*, **11**, 582–591.

SCHUBERT T, JERUSALEM F, MARTENET A-C, METAXAS M, MEYER M (1980) Myotonic dystrophy—early detection and genetic counselling. *Journal of Neurology*, **223**, 13–22.

SHUTLER G, MACKENZIE AE, BRUNNER H, WIERINGA B, DEJONG P, LOHMAN FP *et al.* (1991) Physical and genetic mapping of a novel chromosome-19 ERCC1 marker showing close linkage with myotonic dystrophy. *Genomics*, **9**, 500–504.

SMEETS HJM, BRUNNER HG, ROPERS HH, WIERINGA B (1989) Use of variable simple sequence motifs as genetic markers: application to study of myotonic dystrophy. *Human Genetics*, **83**, 245–251.

SMEETS HJM, HERMENS R, BRUNNER HG, ROPERS HH, WIERINGA B (1991) Identification of variable simple sequence motifs in 19q13.2-qter: markers of the myotonic dystrophy locus. *Genomics*, **9**, 257–263.

STREIB EW, SUN SF (1983) Distribution of electrical myotonia in myotonic muscular dystrophy. *Annals of Neurology*, **14**, 80–82.

STREIB EW, FINE B, SUN F, AITA JF (1987) Myotonic dystrophy sine myotonia: normal EMG in two obligate gene-carriers of advanced age. *Electromyography and Clinical Neurophysiology*, **27**, 443–446.

VEILLETTE S, PERRON M, MATHIEU J (1989) Myotonic dystrophy. II. Marital status, fertility and gene transmission. *Canadian Journal of Neurological Sciences*, **16**, 114–118 (in French).

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EVENT-RELATED POTENTIALS RELATED TO RECOGNITION MEMORY

EFFECTS OF UNILATERAL TEMPORAL LOBECTOMY AND TEMPORAL LOBE EPILEPSY

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SUMMARY

Event-related potentials (ERPs) were recorded during a continuous recognition memory task for visually presented words, with a 6 item lag between the first and second presentation of each word. The subjects consisted of. (i) a control group of patients with primary generalized epilepsy; (ii) patients who had undergone either a left or a right anterior temporal lobectomy; (iii) unoperated patients with either left or right unilateral temporal lobe epilepsy. In the controls, ERPs to detected 'old' words were reliably more positive-going in the interval 300 to 600 ms post-stimulus than were ERPs to 'new' items. In both left and right lobectomy patients, 'old/new' ERP differences in the same latency range were significantly smaller than in the controls, and did not differ significantly from zero. At midline electrodes, old/new effects in the temporal lobe epilepsy patients were of similar magnitude to those of the controls. In contrast to the control data, the old/new effects in the temporal lobe epilepsy patients were asymmetric, in that they were smaller over the hemisphere ipsilateral to the seizure focus than over the contralateral hemisphere. No relationship was found across subjects between the magnitude of old/new ERP effects and verbal memory performance. In a second task, occasional non-words had to be discriminated against a background of sequentially presented words, some of which were repetitions of the immediately preceding item. ERPs evoked by repeated words were more positive-going than were those to first presentations; this effect was reliable, and of equivalent size, in all patient groups.

It is concluded that in the recognition task, old/new ERP effects are dependent on temporal lobe functioning, but that the anterior temporal lobe is not the principal locus of the generators of these effects. The cognitive processes reflected by these effects do not appear to be strongly lateralized to one hemisphere, and neither do they seem to be necessary for normal verbal memory.

INTRODUCTION

A number of studies have described differences between event-related brain potentials (ERPs) evoked by correctly detected 'new' and 'old' words in recognition memory tasks (Karis *et al.*, 1984; Johnson *et al.*, 1985; Neville *et al.*, 1986; Rugg and Nagy, 1989; Smith and Halgren, 1989; Bentin and Moscovitch, 1990; Friedman, 1990). These differences take the form of greater positivity in ERPs to old than in those to new items,

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and appear to result from the modulation of at least two dissociable ERP components: a negative wave peaking around 400 ms (N400); and a subsequent late positive complex, comprising a deflection peaking around 600 ms (P600) and a subsequent slow wave lasting for approximately another 200 ms (Rugg and Nagy, 1989; Smith and Halgren, 1989; Friedman, 1990). The first of these components appears to be sensitive to the old/new status of words only when the lag between study and test is relatively brief, while P600 differentiates old and new items over study/test intervals of at least 45 min (Rugg and Nagy, 1989).

The primary significance of 'old/new' ERP effects in recognition memory tasks lies in the fact that the effects might offer a non-invasive means of studying, with high temporal resolution, brain activity associated with memory formation and/or retrieval. This possibility is strengthened by two sets of findings suggesting that these effects reflect some aspects of the functioning of the temporal lobe, an area of the brain well known to be important for memory. Smith *et al.* (1986) and Heit *et al.* (1990) recorded ERPs from medial temporal lobe (MTL) structures while their patients performed a recognition memory task, and observed large amplitude waveforms which differentiated old and new words over much the same time-frame as did scalp waveforms. These intracerebral old/new effects varied in amplitude and polarity over small distances within and adjacent to the hippocampal formation and amygdala, suggesting that the effects were generated in or close by these structures. It is not known to what extent these intracerebral ERP effects are volume-conducted to the scalp, and hence contribute to scalp waveforms. The effects are important nonetheless, as they demonstrate that activity in a brain region known to be critical for normal memory function discriminates old and new items during the kinds of recognition task that evoke old/new ERP effects on the scalp.

Other work has provided more direct evidence that old/new ERP effects recorded from the scalp are dependent on temporal lobe function. Smith and Halgren (1989) recorded ERPs during a recognition memory task from patients who had undergone left or right anterior temporal lobectomy. The right lobectomy patients' old/new effects were comparable with those of the controls, whereas the effects in the left-sided group did not differ from zero. Importantly, the absent old/new effects in the left lobectomy group were associated with only a mild impairment on the experimental task. Smith and Halgren (1989) accounted for this by suggesting that old/new ERP effects reflect brain activity underlying only one of the means by which recognition judgements can be made, namely the formation and retrieval of episodic memories (*see also* Halgren and Smith, 1987). They suggested that the absence of the ERP effects in their left lobectomy patients was because the patients were unable effectively to form and/or retrieve episodic memories about words' prior presentations, but were able to make recognition judgements on the basis of differences in the 'perceptual fluency' of old and new items (e.g. Jacoby and Dallas, 1981). Hence according to this hypothesis, absent or abnormally small old/new ERP effects in verbal recognition memory tasks should be associated with poor episodic memory for words. Previous work has already provided difficulties for this hypothesis (Rugg and Nagy, 1989; Potter *et al.*, 1991). The present study allows it to be subjected to further scrutiny.

The present study replicates and in two ways extends Smith and Halgren's (1989) findings. First, in addition to studying groups of left and right lobectomy cases, we also investigated unoperated patients suffering from epileptic seizures originating in one temporal lobe. Approximately 65% of such patients have structural pathology (varying in severity) in the hippocampal formation (Babb and Brown, 1987). The anatomically restricted nature of this pathology stands in contrast with the lesion resulting from anterior temporal lobectomy, a procedure which typically involves removal not only of anterior hippocampus, but also of adjacent medial cortex, as well as the amygdala and anterior regions of basolateral cortex. The extent of this resection means that although abnormal old/new ERP effects in anterior lobectomy patients undoubtedly implicate the temporal lobes in the generation of these effects, this finding alone does not allow the relative importance of different temporal lobe structures to be assessed. Abnormal effects in a high proportion of unoperated temporal lobe epilepsy patients would imply that it is the medial regions of the temporal lobe that are most critical for the generation of these effects, and would thus aid the interpretation of the lobectomy data.

The second way in which the present study goes beyond that of Smith and Halgren (1989) is through the use of more than one experimental task. In addition to continuous recognition, we included a second task involving word repetition, which also gives rise to large and robust old/new effects in normal subjects (e.g. Nagy and Rugg, 1989). This second task allowed the investigation of old/new ERP effects in a situtation of minimal demand on memory. If old/new effects in the two tasks share the same intracerebral generators, abnormal effects in one of the tasks should be accompanied by abnormal effects in the other.

METHODS

Subjects

Five groups of patients were employed, one of which served as the control group. Patients in the remaining four groups all had some degree of temporal lobe dysfunction or pathology. (The patients described below were those in whom ERPs were recorded during the recognition memory procedure. As noted later, the patients who also undertook the 'repetition' procedure did not overlap completely with those carrying out the recognition task.)

The controls consisted of 15 patients with idiopathic generalized epileptic syndromes (juvenile myoclonic epilepsy, juvenile absence epilepsy; epilepsy with generalized tonic clonic seizures on awakening). These syndromes are not associated with any structural brain pathology. The patients (who will be referred to collectively as the primary generalized control group) had appropriate generalized EEG abnormalities without focal features. All were taking anti-convulsant medication.

Two groups of patients who had undergone unilateral anterior temporal lobectomy for the relief of intractable epileptic seizures were also studied. In all cases, the operation involved the removal of the anterior 5–6 cm of one temporal lobe, including lateral and medial structures. In some patients, an *en bloc* procedure was used (Falconer, 1971), and in others a two-stage resection was performed, in which medial structures, including amygdala and hippocampus, were removed under the microscope after resection of the lateral and inferior cortex. Eight of the lobectomy patients had received a left-sided, and 8 a right-sided operation. All were receiving anti-convulsants at the time of testing, and were studied at least 3 mths after their operation.

Temporal lobe epilepsy patients formed a further two groups. All the patients experienced complex partial seizures. The clinical features, and the neuroradiological and interictal EEG abnormalities, indicated a temporal lobe origin, which was classified as probable left in 14 patients, and probable right in 11.

Relevant characteristics of each of the above groups are given in Table 1. As can be seen from the table, the groups were reasonably well matched on two tests of verbal function that do not make demands on episodic memory, namely digit span and the vocabulary subtest of the Wechsler Adult Intelligence Scale (Revised) (WAIS-R). ANOVAs comparing the scores of the control and lobectomy groups on these tests were non-significant. By contrast, ANOVA of the same groups' scores on a test of verbal episodic memory,

TABLE 1 CHARACTERISTICS OF EACH PATIENT GROUP

	n	*Age (yrs)*	*Sex (No. of M)*	*Onset (yrs)*	*Hand*	*PA*	*DS*	*Vocab*
P Gen	15	27.6	8	11.1	11	8.5	7.7	8.5
SD		7.2		4.6		2.9	1.5	2.1
Range		17–42		1–19		2–12	5–10	5–11
L Lob	8	24.0	6	6.5	8	4.3	8.0	7.0
SD		7.1		2.7		4.6	2.0	1.8
Range		17–36		2.5–11		0–12	6–12	5–11
R Lob	8	28.6	5	13.8	6	7.7	8.5	9.0
SD		6.8		7.2		3.4	1.5	1.6
Range		21–40		6–25		2–11	7–11	7–12
L Epil	14	23.7	11	10.7	12	7.2	7.9	8.0
SD		5.8		7.3		3.5	2.3	1.7
Range		17–32		1–23		0–11	4–13	5–10
R Epil	11	28.6	5	13.3	9	6.1	8.7	8.4
SD		7.1		9.3		3.6	1.4	1.7
Range		20–41		1–31		1–10	6–11	7–11

P Gen = Primary generalized, L Lob = left lobectomy; R Lob = right lobectomy; L Epil = left temporal lobe epilepsy; R Epil = right temporal lobe epilepsy; Onset = age of first seizure (years); Hand = number of right-handers, PA = raw score on hard paired associates items on the Wechsler Memory Scale (Revised); DS = raw score on digit span subtest on the Wechsler Memory Scale (Revised), Vocab = scaled score on the vocabulary subtest of the Wechsler Adult Intelligence Scale (Revised).

the hard paired-associate items from the Wechsler Memory Scale (Revised) (WMS-R), gave rise to a significant effect [$F(2,27) = 3.65, P < 0.05$], reflecting the relatively poor performance of the left lobectomy patients.

Experimental procedures

Tasks. Two tasks were employed: a continuous verbal recognition memory task (henceforth the 'recognition' task), and a word/non-word discrimination task, in which a proportion of words were repeats of preceding items (the 'repetition' task). No words were employed in more than one of the tasks. The tasks described are in each case the second of two variants employed over the course of the study. Initially, each of the tasks employed two inter-item lags, with the aim of comparing old/new ERP effects as a function of lag (the additional lags were of 19 intervening items in the recognition task, and 6 intervening items in the repetition task). The tasks were modified after the first 21 subjects had been run by the removal in each case of the items associated with the longer of the two lags. These modifications were made because it became clear that ERP effects at the longer lags were highly variable, even among controls, and thus contributed little to the study By removing the longer lag conditions, the duration of the tasks was approximately halved, greatly improving their acceptability to the subjects. There was no evidence of any differences between the data from the two versions of each of the tasks.

The recognition task consisted of the presentation of a list of 224 common English words. Ten of these were filler items, which appeared only once and served to 'pad' the end of the lists, while the remainder were each presented twice. The second presentation of a word was separated from its first occurrence by 6 intervening items. The task was to discriminate between words being shown for the first (new items) and second (old items) time, pressing a microswitch push button with the right index finger for 'old' responses, and with the left index finger for 'new' responses.

The repetition task involved the presentation of a list of 300 items. Two hundred and forty of these were words, of which 50 were repetitions of the immediately preceding word, and 60 were pronounceable non-words. The task was to respond promptly only to the non-words, by pressing a microswitch held in the right hand, and to pay no attention to the repeating words

ERPs from the repetition procedure were obtained in 9 controls (one of whom had not participated in the recognition task), 8 left lobectomy patients (all of whom had also carried out the recognition task), 8 right lobectomy patients (one of whom had not undertaken the recognition procedure), 11 left epilepsy patients (one of whom had not undertaken the recognition procedure) and 10 right epilepsy patients (all of whom had also performed the recognition task).

For both tasks, the stimuli were presented on a TV monitor for a duration of 300 ms within a window subtending a visual angle of approximately 2×0.5 deg. In the recognition task, the inter-stimulus interval (ISI) varied with reaction time (RT) between a minimum of 3.2 s and a maximum of 7.2 s, with response latencies of less than 250 ms or greater than 5 s scored as errors. In the repetition task, the ISI was 3.2 s, and the response window extended from 250 ms to 1600 ms. In both tasks, a fixation asterisk was present other than for the period beginning 150 ms before stimulus onset until 924 ms thereafter. Subjects were instructed to refrain from blinking or making other eye-movements when the asterisk was absent. They were given practice on each task with short lists containing items different from those used in the experimental lists.

EEG recording

EEG was recorded with silver/silver chloride electrodes from 5 scalp sites (Fz, Cz, Pz, T3, T4), referenced to a balanced sterno-vertebral electrode pair (Stephenson and Gibbs, 1951). Bipolar EOG was recorded from electrodes placed on the outer canthus of the left eye and on the supra-orbital ridge of the right eye. All channels were amplified with a bandwidth of 0.03–30 Hz (3 dB points). They were sampled on-line at 4 ms/point for a 1024 ms epoch beginning 100 ms before stimulus onset. Any trials containing EOG artefact were excluded from average ERPs. In the recognition task, separate ERPs were formed for correctly classified 'old' and 'new' words. In the repetition task separate ERPs were also formed for old and new words, again using only error-free trials.

RESULTS

In order to allow a direct comparison with the findings of Smith and Halgren (1989), the primary analyses take the form of comparisons between the lobectomy patients and the controls. The data from the epilepsy patients, whose ERP data from the recognition task are more heterogeneous than those of the other groups (as might be expected in view of the variable nature of their pathology; *see* Introduction), are subjected to a separate set of statistical analyses. Unless otherwise specified, analyses are based on mixed design ANOVAs. Unequal group sizes were dealt with by the method of unweighted means, and the degrees of freedom of within-subjects factors comprising more than two levels were subjected to the Geisser-Greenhouse correction (Jennings and Wood, 1976). In the accounts of the results of ANOVAs on ERP data, description of the electrode site main effect (which is almost invariably significant) is omitted, as it is of no experimental interest in the absence of an interaction with some other factor.

Recognition task

Behavioural performance: RT, accuracy, and response bias (the index Br, as recommended by Snodgrass and Corwin, 1988) are shown for all patient groups in Table 2. Comparison of the RTs of the control and lobectomy groups revealed no significant effects. And although Table 2 shows a trend toward lower accuracy on the part of the left lobectomy patients, group differences in accuracy (assessed with the index pHit-pFalse Alarm) did not approach significance [$F(2,28) = 1.36$]. However, ANOVA of the response bias index Br did reveal a significant group effect [$F(2,28) = 3.96$, $P < 0.05$], reflecting a more conservative response bias in the controls than in the lobectomy groups.

In the case of the temporal lobe epilepsy patients, ANOVA gave rise to no significant effects with respect to RT or accuracy. As with the lobectomy group, ANOVA of the

TABLE 2 PERCENT CORRECT, REACTION TIME AND RESPONSE BIAS FOR EACH PATIENT GROUP ON THE RECOGNITION MEMORY TASK

	New words		*Old words*		
	% corr	*RT (ms)*	*% corr*	*RT (ms)*	*Br*
P Gen	94.7	824	81.8	859	0.213
SD	6.3	137	11.4	186	0.214
L Lob	84.2	943	83.1	944	0.459
SD	11.2	231	9.7	238	0.254
R Lob	91.3	1027	85.9	1017	0.415
SD	6.7	332	11.6	285	0.254
L Epil	86.3	951	90.9	876	0.594
SD	8.7	341	7.5	213	0.198
R Epil	85.2	889	88.3	852	0.592
SD	11.1	184	12.7	128	0.169

P Gen = primary generalized; L Lob = left lobectomy; R Lob = right lobectomy; L Epil = left temporal lobe epilepsy; R Epil = right temporal lobe epilepsy; RT = reaction time, Br = response bias

response bias data led to a significant group effect [F(2,37) = 17.46, $P < 0.001$], again the result of a conservative response bias on the part of the controls.

Grand average ERPs evoked by correctly classified new and old words from the three midline sites are illustrated in Fig. 1, and the grand averages of the waveforms from the temporal electrodes are shown in Fig. 2. Averaged over the two conditions, the mean number of trials (and lower end of the range) used to form the individual subjects' averages were 82 (36), 78 (54), 85 (42), 78 (36) and 81 (52), for the control, left lobectomy, right lobectomy, left epilepsy and right epilepsy patients, respectively. Following initial N120 and P200 components, ERPs evoked by new words exhibit a broad negative-going deflection, peaking around 400 ms (N400), followed by a slow parietal-maximum positive-going wave, peaking around 650 ms (P600). In the case of the controls, ERPs to old words are, in comparison with those to the new items, more positive-going from around 250 to 300 ms post-stimulus. Similar old/new effects can be seen in the grand averages of the temporal lobe epilepsy patients, but these effects are much less in evidence in the waveforms of the two lobectomy groups, especially in the region 300–600 ms post-stimulus.

To capture the early and late regions of the old/new effects evident in Figs 1, 2, the mean amplitudes (with respect to the mean of the pre-stimulus baseline) of two latency regions, 300–600 ms and 600–900 ms were subjected to analysis. Measurement of the mean amplitude of fixed latency regions is a common practice in cognitive ERP studies. The procedure has the benefits of being objective and of providing measures which, because they are derived from a substantial number of sampling points, are relatively unaffected by residual noise. The earlier of the two regions reported here (300–600 ms) is comparable with the single region reported by Smith and Halgren (1989), which extended from 250 to 650 ms. The earlier of these regions straddles the N400 deflection, whereas the later region encompasses the P600 and subsequent slow wave. These data are shown in Tables 3, 4 for all groups, and individual subjects' 300–600 ms data, collapsed over the midline electrode sites, are illustrated in Fig. 3.

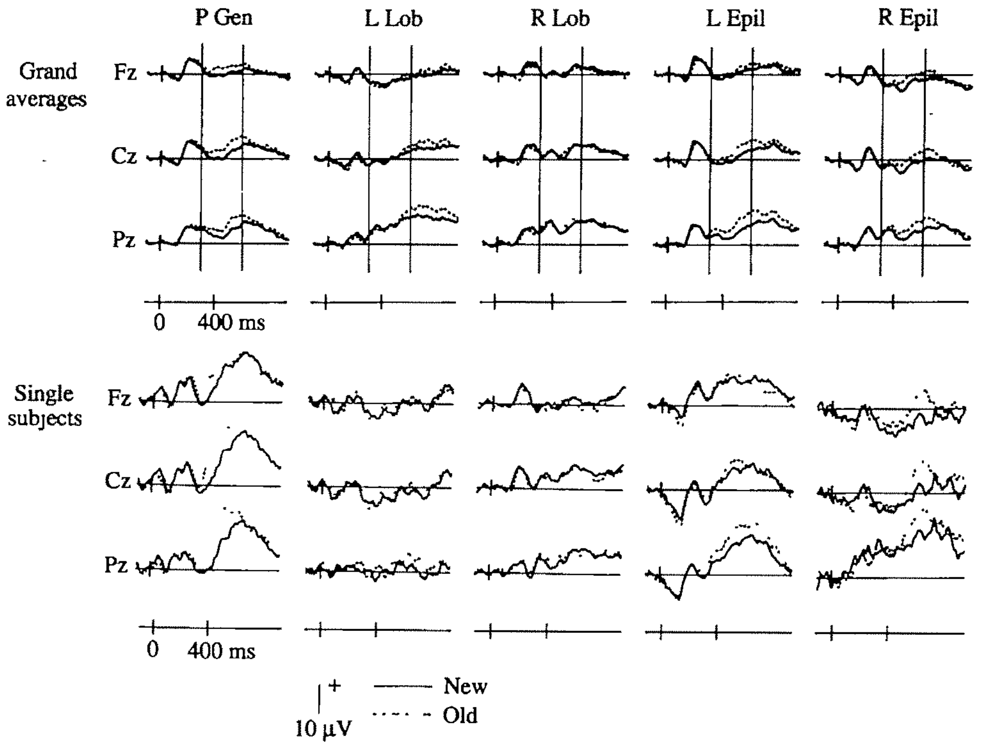

FIG. 1. *Upper panel*: grand average waveforms, evoked by correctly classified 'new' and 'old' words in the recognition procedure, from the midline electrodes of the subjects in each patient group. Vertical lines indicate the 300–600 ms latency region P Gen = primary generalized controls, L Lob = left lobectomy patients, R Lob = right lobectomy patients; L Epil = left temporal lobe epilepsy patients, R Epil = right temporal lobe epilepsy patients. *Lower panel*: waveforms from the recognition task in representative single subjects from each patient group.

In order to maximize the power of interhemispheric contrasts, separate ANOVAs were conducted on the data from the midline and the temporal electrode sites. In each case these ANOVAs employed the factors of group, word type (old vs new words) and electrode site.

ANOVA of the 300–600 ms data from the midline electrodes of the control and lobectomy groups gave rise to a significant main effect of word type [$F(1,28) = 11.22$, $P < 0.002$], and to a significant interaction between word type and group [$F(2,28) = 5.70$, $P < 0.01$]. All interactions with the factor of electrode site were non-significant. As can be seen from Table 3, the word type by group interaction reflects smaller old/new effects in the two lobectomy groups than in the controls. *Post-hoc* tests (Tukey HSD) showed that while the controls' old/new effects were reliable ($P < 0.01$), those of the lobectomy patients were not.

ANOVA of the 300–600 ms data from the lateral sites of the control and lobectomy patients gave rise to only one reliable effect, the interaction between word type and group [$F(2,28) = 5.20$, $P < 0.025$]. As with the analysis of the midline electrodes,

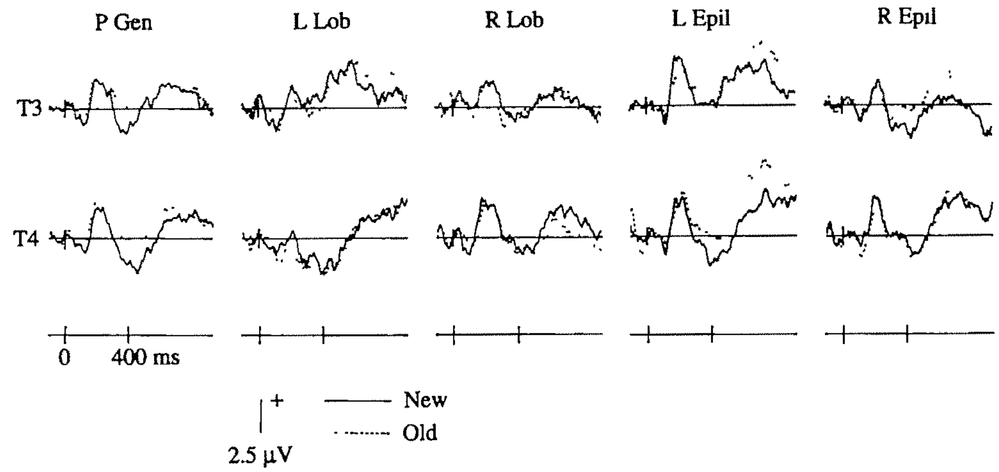

FIG 2. Grand average waveforms, evoked by correctly classified 'new' and 'old' words in the recognition procedure, from the left (T3) and right (T4) temporal electrodes of each patient group. Abbreviations as in Fig. 1. Note the change of amplitude scale from that figure.

this reflected larger old/new effects in the controls than in either of the two lobectomy groups.

Analysis of the 600−900 ms data from the controls and lobectomy patients gave rise to only one significant effect, the interaction between word type and electrode site [F(1.3,37.2) = 7.69, P = 0.005]. This reflected the parietal maximum of the old/new effects in this region of the waveform. Although the data in Table 4 suggest that the three groups differ with respect to the size of these effects (which are larger than those of the controls in the left lobectomy patients, but apparently absent in the right lobectomy group), no hint that these differences were reliable emerged from the ANOVA [group by word type: F(2,28) = 1.60; group by word type by site: F(2.7,37.2) = < 1.0]. ANOVA of the 600−900 ms data from the lateral sites revealed no significant effects.

The old/new effects in the 300−600 ms latency region in the temporal lobe epilepsy patients are more variable than those of either the control or the lobectomy groups. As can be seen from Table 3 and Fig. 3, however, the mean size of the old/new effects in these patients is similar to that of the controls. ANOVA of these data gave rise to a reliable effect of word type [F(1,37) = 32.41, $P < 0.001$], as well as to a reliable interaction between word type and electrode site [F(1.5,55.6) = 9.10, $P < 0.01$], which reflected the centroparietal maximum of the old/new effect.

In the case of the 300−600 ms data from the temporal electrodes, a reliable effect of word type [F(1,37) = 11.75, P = 0.002] was found, along with a significant three-way interaction between group, word type and electrode site [F(2,37) = 4.10, P = 0.025]. This interaction appears to reflect differing patterns of asymmetry in the old/new effects from each group. As can be seen in Fig. 2, whereas the effects are almost symmetrical in the case of the controls (left site = 1.56 μV, right site = 1.60 μV), they tend to be larger over the right than the left hemisphere in the left epilepsy patients (0.89 μV vs 1.84 μV), and vice-versa in the right epilepsy group (1.29 μV vs −0.17 μV). In support of this interpretation, ANOVA on the data solely from the two temporal

TABLE 3 MEAN AMPLITUDE (MICROVOLTS) OF THE 300–600 MS LATENCY REGION OF THE ERPs EVOKED BY CORRECTLY CLASSIFIED OLD AND NEW WORDS IN THE RECOGNITION TASK

	Fz	*Cz*	*Pz*	*LT*	*RT*
P Gen					
New	−1.33	0.50	3.87	−0.39	−1.26
SD	9.06	6.70	5.20	5.16	6.23
Old	0.88	3.54	6.72	1.16	0.34
SD	8.90	6.41	5.47	4.90	5.90
Old−New	2.21	3.04	2.85	1.56	1.60
SD	1.50	2.00	2.13	1.54	1.36
L Lob					
New	−2.56	0.42	6.94	1.95	−1.40
SD	3.82	3.01	5.84	4.53	2.97
Old	−2.34	0.59	7.36	1.35	−1.71
SD	3.78	3.97	6.49	3.53	2.54
Old−New	0.22	0.17	0.43	−0.60	−0.31
SD	1.95	2.12	1.49	2.14	1.81
R Lob					
New	1.09	2.74	6.40	−0.14	−0.23
SD	5.90	4.46	3.79	3.48	6.09
Old	0.80	3.24	7.30	−0.24	−0.58
SD	5.64	3.57	3.52	2.96	6.83
Old−New	−0.29	0.50	0.90	−0.10	−0.35
SD	2.04	2.25	2.33	1.83	2.56
L Epil					
New	0.11	0.53	4.18	1.12	−0.75
SD	7.63	7.04	6.50	4.35	4.70
Old	1.34	2.92	7.27	2.01	1.08
SD	6.39	5.31	5.29	2.98	3.66
Old−New	1.23	2.39	3.09	0.89	1.84
SD	2.79	3.39	2.95	2.52	2.65
R Epil					
New	−3.29	−2.17	4.04	−1.18	−0.09
SD	11.66	9.75	6.16	7.44	5.69
Old	−1.43	0.06	6.11	0.11	−0.27
SD	10.07	8.67	7.41	6.66	6.10
Old−New	1.87	2.23	2.07	1.29	−0.17
SD	2.94	3.46	3.00	2.56	3.53

P Gen = primary generalized; L Lob = left lobectomy, R Lob = right lobectomy; L Epil = left temporal lobe epilepsy, R Epil = right temporal lobe epilepsy

lobe epilepsy groups gave rise once again to a significant three-way interaction [$F(1,23) = 5.08$, $P < 0.05$].

As can be seen in Table 3, the variance of the old/new effects in the temporal electrodes of the control and temporal lobe epilepsy groups is heterogenous, especially in the case of the measures from the right hemisphere, thus calling into question the reliability of the findings from the ANOVAs. A distribution-free approach to the question of whether these three groups showed differing patterns of hemisphere asymmetry in their old/new effects was therefore also employed. This involved a test of association between group membership and direction of hemisphere asymmetry of the old/new effect. In 8/15 control patients old/new effects were larger from the left than the right hemisphere; the same

TABLE 4 MEAN AMPLITUDE (MICROVOLTS) OF THE 600–900 MS LATENCY REGION OF THE ERPs EVOKED BY CORRECTLY CLASSIFIED OLD AND NEW WORDS IN THE RECOGNITION TASK

	Fz	*Cz*	*Pz*	*LT*	*RT*
P Gen					
New	−0.83	2.41	4.94	1.27	1.56
SD	9.17	7.96	7.01	4.66	5.29
Old	−0.34	3.62	6.57	1.77	1.81
SD	8.71	7.47	7.38	4.69	5.11
Old−New	0.48	1.22	1.63	0.50	0.25
SD	2.77	3.03	3.31	1.86	1.67
L Lob					
New	0.47	4.23	9.35	1.38	1.73
SD	5.66	4.27	5.68	4.93	3.95
Old	1.64	6.04	12.49	2.50	1.78
SD	5.77	5.56	8.18	4.58	6.03
Old−New	1.17	1.81	3.14	1.12	0.05
SD	3.84	3.42	3.25	3.63	3.07
R Lob					
New	1.39	3.54	7.00	0.49	1.53
SD	4.31	4.24	3.15	3.18	4.62
Old	0.27	3.19	7.22	0.25	0.26
SD	3.68	5.55	5.73	1.65	6.24
Old−New	−1.12	−0.35	0.22	−0.25	−1.27
SD	2.08	3.93	3.69	2.10	2.69
L Epil					
New	2.31	3.97	7.45	2.22	2.54
SD	6.22	6.33	5.80	5.07	4.26
Old	3.19	5.52	10.20	4.13	4.72
SD	5.38	6.59	5.90	4.31	3.38
Old−New	0.88	1.55	2.75	1.91	2.18
SD	3.41	3.91	3.73	3.56	3.23
R Epil					
New	−2.36	−0.36	5.67	−0.26	2.34
SD	14.29	12.69	8.54	8.68	5.30
Old	−1.68	0.50	6.78	0.08	2.41
SD	13.66	13.78	10.67	9.68	5.84
Old−New	0.68	0.86	1.11	0.34	0.08
SD	4.15	4.98	4.72	3.80	4.02

P Gen = primary generalized; L Lob = left lobectomy; R Lob = right lobectomy, L Epil = left temporal lobe epilepsy, R Epil = right temporal lobe epilepsy.

asymmetry occurred in 4/14 left epilepsy patients, and in 9/11 right epilepsy patients. A chi-square test indicated that these frequency distributions differed reliably from chance ($\chi^2 = 7.01$, df = 2, $P < 0.05$). A second test, performed on the temporal lobe epilepsy patients' data only, was also reliable ($\chi^2 = 7.00$, df = 1, $P < 0.01$). These analyses thus confirm the findings of the ANOVA, in that they indicate the existence of a significant association between side of epileptic focus and asymmetry of the old/new effect in the recognition procedure.

ANOVA of the 600–900 ms region of the control and temporal lobe epilepsy patients' ERPs yielded a reliable effect of word type [$F(1,37) = 4.80$, $P < 0.05$], and a word type by electrode site interaction [$F(1.4,51.2) = 5.84$, $P < 0.025$], but no interactions

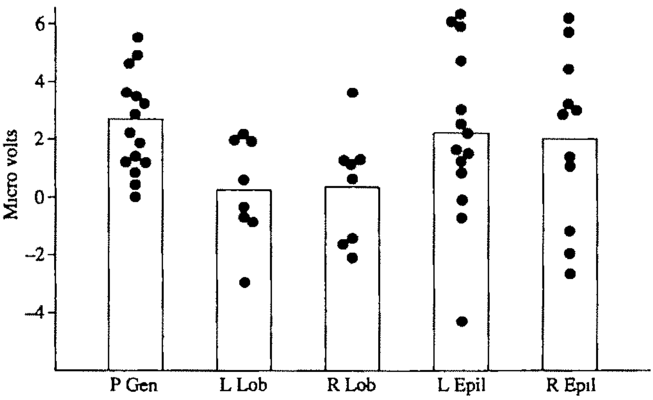

FIG 3 Histograms illustrating the mean old/new effect in the recognition task in the 300−600 ms latency range, averaged over the three midline electrodes, for each patient group. The points superimposed on the histograms indicate the data for each group member. Abbreviations as in Fig. 1.

with group. Analysis of these data from the temporal sites gave rise to no significant effects.

In summary, the old/new ERP effects in the 300−600 ms latency region are abnormally small in the two lobectomy groups. The effects are on average of normal size, although more variable, in the two temporal lobe epilepsy groups, the scores in which overlap considerably with those of the lobectomy patients. Independent tests of the significance of the old/new effects from the midline electrodes in the 300−600 ms latency range are consistent with these conclusions. The tests were significant in the case of the control and the left and right temporal lobe epilepsy patients [$F(1,14) = 38.81$, $F(1,13) = 7.95$, and $F(1,10) = 5.15$, respectively], but not in the case of the lobectomy patients [$F(1,7) < 1$ for both groups]. In order to boost power, a further test was conducted on the data pooled across the two lobectomy groups. This also indicated that these patients' old/new effects did not differ from zero [$F(1,15) < 1$].

The question of whether the old/new effects of the lobectomy patients were smaller than those of the subjects with temporal lobe epilepsy was addressed with a distribution-free test. This test was based on the number of patients in each group (collapsed over side of pathology) whose old/new effects exceeded the mean old/new effect of the control group (2.7 μV, collapsed over midline sites). As can be seen in Fig. 3, old/new effects exceeded the control mean in 11/25 temporal lobe epilepsy patients, a proportion that would be expected if these patients' scores were distributed symmetrically around the same central location as that of the control group. By contrast, only 1/16 lobectomy scores exceeded the control mean. A chi-square test indicated that these differing proportions are unlikely to have occurred by chance ($\chi^2 = 6.72$, $P < 0.01$). Thus old/new effects in lobectomy patients are more likely to be small (relative to controls) than are the effects in patients with temporal lobe epilepsy.

Relationship of old/new effects to memory: the relationship between the size of the old/new effects in the recognition task and verbal memory performance was assessed by correlating the effects (collapsed over midline electrode sites) with (i) accuracy on the task and (ii) performance on the hard paired-associates of the WMS-R (*see* Table 1). Both correlation coefficients were small and non-significant (r54 = 0.091 and r53 = 0.121, respectively; the correlation between the two measures of memory was highly reliable, r53 = 0.580, $P < 0.001$).

Various other correlation and regression analyses were also performed in order to search for factors that might be predictive of the magnitude of old/new ERP effects (e.g. age, gender, clinical features, psychometric scores, task RT, etc.). Group membership was the only variable to account for a significant proportion of the variance in the size of old/new ERP effects.

Repetition task

The behavioural data on the repetition task are shown for each group in Table 5. As in the recognition task, the lobectomy and temporal lobe epilepsy patients' data were compared with those of the controls in separate analyses. Group differences in RT, proportion of correctly detected non-words, and proportion of false positive responses were all non-significant.

TABLE 5 MEAN RT, PERCENT CORRECT, AND PERCENT FALSE POSITIVE RESPONSES FOR EACH PATIENT GROUP ON THE REPETITION TASK

	RT (ms)	*% correct*	*% false positives*
P Gen	912	74.0	4.1
SD	144	14.9	3.7
L Lob	947	70.0	7.7
SD	162	25.5	8.2
R Lob	919	79.6	1.8
SD	163	26.4	1.8
L Epil	864	80.5	2.5
SD	138	17.3	2.3
R Epil	921	83.8	2.4
SD	109	10.8	1.7

P Gen = primary generalized, L Lob = left lobectomy; R Lob = right lobectomy; L Epil = left temporal lobe epilepsy; R Epil = right temporal lobe epilepsy

Grand average waveforms evoked by old and new items on this task are shown in Fig. 4. In all groups, ERPs evoked by old items are more positive-going than are those to new words from approximately 300 ms post-stimulus. The reliability of this effect was assessed by measuring the mean amplitude of the 300–600 ms latency region. These data are shown in Table 6 and, collapsed over midline electrode sites, in Fig. 5. As can be seen from that figure, in every group the majority of the patients exhibited a positive-going old/new effect.

ANOVA of the repetition data from the midline electrodes of the controls and lobectomy patients gave rise to significant effects for word type [$F(1,22) = 46.27$, $P < 0.001$] and for the interaction between word type and electrode site [$F(1.3,28.7) = 4.90$, $P < 0.05$]. The former effect reflects the large old/new differences evident in the

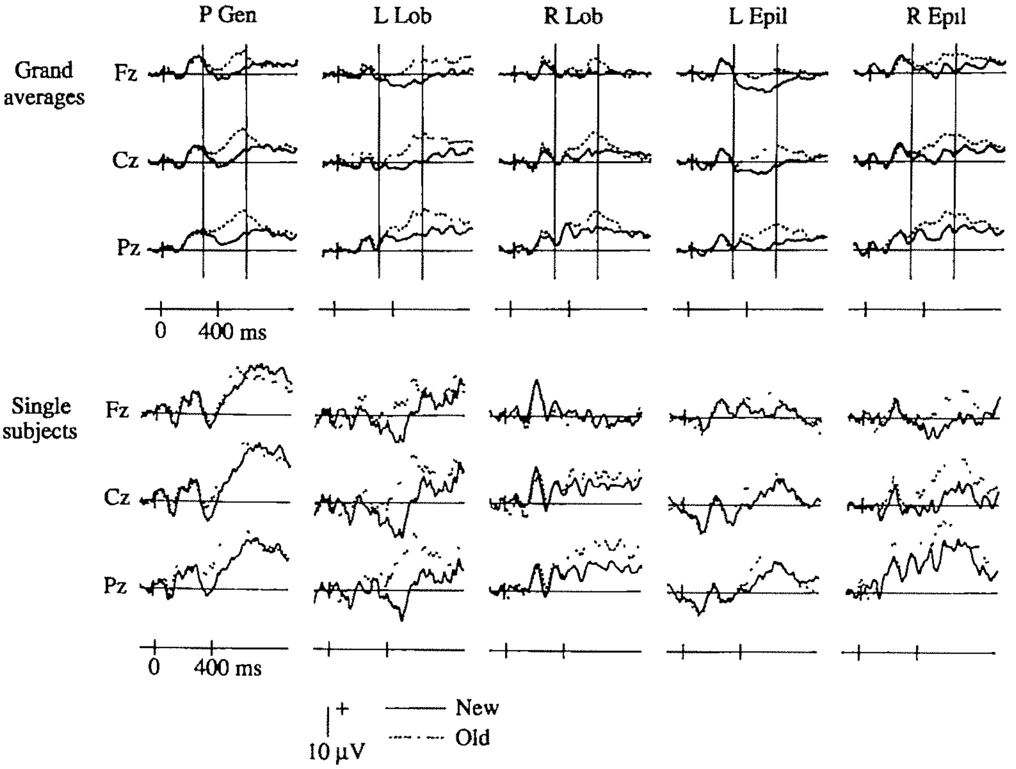

FIG. 4 *Upper panel*: grand average waveforms, evoked by 'new' and 'old' words in the repetition procedure, from the midline electrodes of the subjects in each patient group. Vertical lines indicate the 300–600 ms latency region. Abbreviations as in Fig. 1 *Lower panel*: waveforms from the repetition task in representative single subjects from each patient group. The waveforms illustrated are from the same subjects as those shown in the lower part of Fig 1.

waveforms, and the latter effect their centro-parietal maximum. The interactions between group and word type, and group, word type and electrode site, were far from significant (Fs of 1.13 and < 1, respectively). As can be seen in Table 6, the corresponding data from the lateral sites are highly variable in the lobectomy patients, especially in the case of the right group. ANOVA on these data revealed just one significant effect, that of word type [F(1,22) = 14.68, P = 0.001].

Comparison of the 300–600 ms data from the midline sites of the temporal lobe epilepsy patients with those of the controls yielded, as above, significant effects for word type [F(1,30) = 71.70, $P < 0.001$] and for the interaction between word type and electrode site [F(1.3,40.2) = 6.55, $P < 0.01$]. The data from the temporal sites were much more variable in the temporal lobe epilepsy groups than in the controls. ANOVA on the data from these electrodes revealed a significant effect of word type [F(1,30) = 34.93, $P < 0.001$].

In summary, the analyses of the ERP data from the repetition task indicate that, compared with the controls, the lobectomy and the epilepsy groups exhibited old/new effects of normal magnitude in the 300–600 ms latency region. Consistent with this

TABLE 6 MEAN AMPLITUDE (MICROVOLTS) OF THE 300–600 MS LATENCY REGION OF THE ERPs EVOKED BY OLD AND NEW WORDS IN THE REPETITION TASK

	Fz	*Cz*	*Pz*	*LT*	*RT*
P Gen					
New	0.32	1.33	4.06	1.10	0.87
SD	4.51	4.03	5.06	3.85	3.20
Old	4.32	7.04	9.69	3.60	4.51
SD	3.88	3.43	5.00	3.42	3.51
Old–New	4.00	5.71	5.64	2.50	3.65
SD	2.61	3.05	3.97	2.62	3.29
L Lob					
New	−2.96	−1.02	4.71	1.80	−0.88
SD	5.77	4.86	5.42	5.38	2.70
Old	1.72	4.81	9.26	4.75	2.81
SD	5.47	5.10	3.91	3.02	4.94
Old–New	4.68	5.83	4.55	2.95	3.69
SD	3.60	3.33	3.46	4.67	5.31
R Lob					
New	−0.11	2.29	6.70	0.30	3.03
SD	6.24	5.85	5.99	3.29	5.73
Old	2.23	6.06	9.63	1.41	3.98
SD	5.30	5.11	5.29	4.65	7.04
Old–New	2.34	3.77	2.93	1.11	0.95
SD	3.91	3.76	3.48	4.50	3.63
L Epil					
New	−4.97	−2.95	1.53	−1.83	−1.82
SD	8.64	7.61	6.92	4.10	4.01
Old	−0.52	2.48	5.83	1.46	1.64
SD	6.94	6.99	6.77	3.16	4.10
Old–New	4.46	5.43	4.30	3.30	3.47
SD	4.55	3.94	3.34	2.55	3.70
R Epil					
New	0.88	1.75	5.40	1.71	2.95
SD	4.44	5.52	5.91	3.01	4.92
Old	4.18	6.46	9.93	3.82	4.92
SD	4.74	5.54	7.26	3.25	3.91
Old–New	3.30	4.71	4.53	2.11	1.97
SD	1.27	2.18	3.10	2.74	5.28

P Gen = primary generalized, L Lob = left lobectomy; R Lob = right lobectomy, L Epil = left temporal lobe epilepsy, R Epil = right temporal lobe epilepsy.

conclusion, separate tests of the significance of these effects from the midline electrodes of each group showed them to be reliable in all cases [F(1,8) = 24.70; F(1,7) = 19.18; F(1,7) = 6.55; F(1,13) = 22.80; F(1,9) = 42.51; for control, left lobectomy, right lobectomy, left temporal lobe epilepsy and right temporal lobe epilepsy groups, respectively]. There was no evidence of any group differences in the asymmetry of the old/new effects from this task.

DISCUSSION

The present findings only partially replicate those of Smith and Halgren (1989). In the recognition task, old/new ERP effects in the left lobectomy group were significantly smaller than those of the controls. But in contrast to Smith and Halgren's (1989) results,

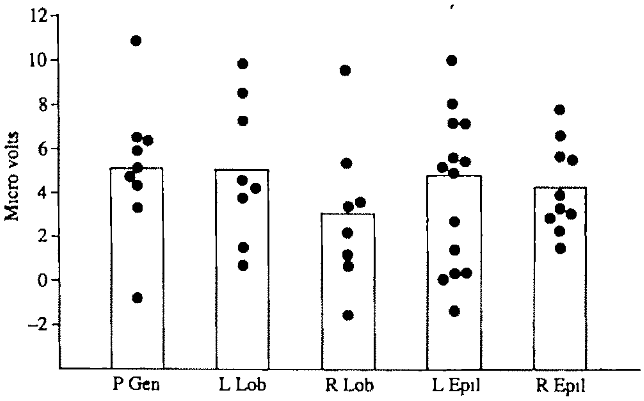

FIG 5. Histograms illustrating the mean old/new effect in the repetition task in the 300–600 ms latency range, averaged over the three midline electrodes, for each patient group The points superimposed on the histograms indicate the data for each group member Abbreviations as in Fig 1.

the right lobectomy group also exhibited attenuated old/new effects. There are at least two possible reasons for this inconsistency. First, the recognition memory tasks employed in the present and previous studies differed. Smith and Halgren (1989) employed a procedure in which a set of 20 words was initially presented for study. A subset of 10 of these words was then repeated in 9 subsequent blocks, intermixed with an equal number of new items unique to each block. The patients were required to respond in each block only to the repeated (i.e. old) words. ERPs to old words were formed by averaging the trials associated with all correctly classified old items, regardless of block. By contrast, the procedure in the present experiment involved continuous recognition, each word being presented twice only and requiring a different response on each occasion. It remains to be seen whether, if each old word was repeated several times in the present procedure, reliable old/new effects would emerge in the right but not the left lobectomy patients. For the same reason it would also be of interest to determine whether, using the procedure employed by Smith and Halgren (1989), right lobectomy patients exhibit an old/new effect when the comparison is between ERPs evoked by new words and those evoked by old words on their first representation.

In addition to differences between the tasks, it is also possible that the patients in the two studies differed in important respects. These differences could have resulted from the employment of different clinical criteria for lobectomy, and/or different surgical procedures. Until these issues and the questions raised in the preceding paragraph are resolved, no generalization is possible about the relationship between the overall magnitude of ERP effects in recognition memory tasks and laterality of temporal lobe pathology.

The absence of a reliable old/new effect in the lobectomy patients' ERPs might reflect a lack of statistical power rather than a genuine null effect. This could arise if the size of the population effect is small relative to the residual noise level of patients' waveforms. The small size of these effects in the lobectomy patients in the present sample (averaging only 0.21 μV over the midline electrodes) suggests that the resolution of this issue will require a very much larger sample of patients than that typically employed in studies of this type. The question of whether lobectomy patients exhibit smaller old/new effects than controls is, however, independent of this issue, and depends instead on the statistical significance of group by word-type interaction effects in the relevant ANOVAs. The reliability of these interactions justifies the conclusion that temporal lobectomy is associated with an attenuation of early old/new effects in the recognition task.

The reduction in size of old/new ERP effects in the lobectomy patients was confined to the 300–600 ms latency region of the ERPs evoked in the recognition task. As noted in the Introduction, the old/new effect in this task appears to reflect the modulation of at least two overlapping ERP components: the N400, and a following late positive complex which is thought to be allied to the well-known 'P3' component and following slow wave. The finding that old/new effects were reliably smaller in the lobectomy patients only in the 300–600 ms latency region, the region encompassing the N400 deflection, could be taken as evidence in support of Smith and Halgren's (1989) suggestion that lobectomy interferes more with the modulation of N400 than with that of the subsequent late positive component. This evidence should, however, be regarded as tentative, in view of the high degree of variance in the late-occurring old/new effects (as indexed by the 600–900 ms latency region), and their apparent absence in the right lobectomy patients. Future work examining this question would do well to employ an experimental manipulation which is known to dissociate old/new effects attributable to N400 and 'P600' [e.g. word frequency (Rugg, 1990) or study-test interval (Rugg and Nagy, 1989)], thereby allowing greater experimental control over the two components.

In contrast to the recognition task, the repetition procedure, in which words were repeated immediately, yielded old/new effects of comparable onset latency and amplitude in the control and lobectomy groups. This dissociation between the two tasks demonstrates that the abnormally small effects observed in the lobectomy patients in the recognition task cannot be attributed to some non-specific disruption of ERP generators sensitive to word repetition. The dissociation could have arisen because the apparently similar old/new effects observed in the two tasks rely on different intra-cerebral generators. For example, it may be that in the version of the repetition task employed here, the balance between the contributions made to the old/new effect by modulation of N400 (affected by lobectomy) and a P3-like component (unaffected by lobectomy; Johnson and Fedio, 1986; Stapleton *et al.*, 1987; Johnson, 1988; Rugg *et al.*, 1991) is shifted in favour of the latter. However, the idea that old/new effects in the repetition procedure are largely the result of the modulation of a late positive component has, for a number of reasons, been found wanting (Rugg *et al.*, 1988; Bentin and Peled, 1990).

An alternative explanation for the dissociation between the two tasks is that they engage different neural systems which while not themselves responsible for generating old/new ERP effects, provide independent sources of input to the generator(s) that *are* responsible. These different systems might be differentially activated in the two tasks by virtue of the fact that the processing of repeated words is intentional in one case (the recognition task) but incidental in the other (the repetition task). Alternatively, the critical difference between the two tasks may merely reflect the fact that in one case repetition was immediate, whereas in the other it was delayed. Either way, it follows that it is only in the recognition task that temporal lobectomy compromises word processing in such a way as to lead to the attenuation of the old/new ERP effect. Therefore by this account, the generators of the effect are unlikely to be located principally in the anterior medial temporal lobe, despite the suggestive nature of the intracerebral data (Smith *et al.*, 1986; Heit *et al.*, 1990).

There were no significant differences between the controls and the lobectomy patients with respect either to recognition accuracy or speed of responding, there being only a tendency for poorer performance on the part of the left-sided patients. As would be expected on the basis of much previous work (*see* Smith, 1989 for a review), the left lobectomy group did, however, exhibit a reliable verbal memory deficit on a measure of paired-associate learning (*see* Table 1). This suggests that the lack of impairment in these patients in the recognition task is more a function of the task's insensitivity to relatively mild memory impairments than of the selection of an atypical patient sample.

There was no relationship between the size of old/new effects in the recognition task and level of performance on either the task itself or on the paired associate test of verbal memory. This is highlighted by the finding that the control and lobectomy groups performed the recognition task with comparable levels of accuracy and response latencies, yet only the controls exhibited reliable old/new effects. Thus the processes reflected by these effects do not appear to be causally related to the ability to perform old/new discriminations during continuous recognition. It has been argued (Smith and Halgren, 1989) that such discriminations can be made in this kind of task on the basis of judgements about the words' relative perceptual fluency, without retrieving the specific instance of the first presentation of each old word from episodic memory. If it is assumed that 'old/new' ERP effects reflect only episodic retrieval, then the apparent paradox of the absence of a 'memory-related' ERP modulation in the face of normal recognition memory performance can be resolved.

Such an account might explain the dissociation between task performance and ERP effects observed here. It is difficult though to see how it can be reconciled with the finding that whereas both lobectomy groups exhibited abnormally small old/new effects, it was only the left-sided group that was impaired on a test of paired associate learning, a test for which the ability to retrieve specific prior episodes would appear essential. In suggesting that there is no direct relationship between old/new ERP effects and the processes subserving episodic memory, the present data contradict the hypothesis of Smith and Halgren (1989), and instead concur with previous work on healthy subjects (Rugg and Nagy, 1989; Potter *et al.*, 1991).

As already noted, in contrast to previous findings (Smith and Halgren, 1989), the present results suggest that abnormally small old/new effects in a recognition memory task can occur after unilateral damage to either temporal lobe. This is a puzzling result whatever the nature of the cognitive processes reflected by these effects, as it seems to imply that they are dependent on some kind of interaction between the two hemispheres. There is, however, a precedent for this result; Knight *et al.* (1989) reported that the P3 wave evoked by rare auditory stimuli in an 'oddball' task is abolished bilaterally by unilateral damage to the temporo-parietal junction of either hemisphere. Knight *et al.* interpreted their findings as implying that the generation of P3 depended on an interaction between critical regions in each hemisphere, either through the corpus callosum (unlikely, in light of the findings of Kutas *et al.*, 1990), or more indirectly, through projections to one or more subcortical structures. An analogous line of reasoning would appear possible in the present case. It will be of interest to see whether other late ERP phenomena are similarly affected by unilateral lesions.

The mean old/new ERP effects of the two temporal lobe epilepsy groups did not differ significantly from those of the controls, although in both groups the distribution of the effects was more variable, 20% of the epilepsy patients exhibiting old/new effects outside the lower 95% confidence limit of the control sample. As with the lobectomy data, there was no indication that abnormally small effects predominated in left-sided patients. The trend was in fact in the opposite direction. Nor were we able to find evidence of an association between the size of the epilepsy patients' old/new effects and any potentially relevant clinical variable (including severity and frequency of seizures, age of seizure onset, and presence/absence of febrile convulsions).

Although the numbers are small, the observation that some temporal lobe epilepsy patients manifest abnormal old/new effects suggests that damage to the temporal lobe need not be as severe as that caused by lobectomy for such abnormalities to occur. Nonetheless, it seems unlikely that the pathology typically associated with temporal lobe epilepsy is sufficient to attenuate old/new ERP effects, at least with the present procedures. This might be because of the anatomically restricted nature of this pathology, which in many patients is confined to the hippocampal formation and immediately surrounding medial temporal cortex (Babb and Brown, 1987). Alternatively, it might be that hippocampal pathology is sufficient to attenuate these effects, but only when it is especially severe. On the basis of the first hypothesis, the patients in the present series with the most abnormal ERP effects would be expected to be those with pathology in temporal lobe structures other than the hippocampus. According to the second hypothesis, these patients would be the ones with the most severe hippocampal pathology. Future research, correlating pre-operative old/new effects with histological data from resected temporal lobe tissue, should resolve this issue.

Although the old/new effects from the recognition task were not reliably smaller in the temporal lobe epilepsy patients than in the controls, they did show different patterns of asymmetry. The controls exhibited old/new effects that, averaged across subjects, were approximately symmetrical. The effects in the temporal lobe epilepsy groups departed from this pattern, there being a tendency for the temporal electrode over the hemisphere with the epileptic focus to yield smaller old/new ERP differences than the electrode over the opposite hemisphere. The size of these asymmetries is small, and they are not present in every patient. Furthermore, it remains to be clearly established that they reflect differences in the functional/structural integrity of the temporal lobes of the two hemispheres, and not merely contamination by lateralized epileptiform EEG activity (this latter possibility does, however, seem remote, as analogous asymmetries were not observed in these patients' ERPs from the repetition task). If the asymmetries in the old/new effects in the recognition task are reproducible, and turn out to be more than just a reflection of interictal EEG abnormalities, they offer a potential avenue for the identification and investigation of lateralized temporal lobe dysfunction. Also, of course, asymmetries in old/new ERP effects resulting from pathology less extensive than that caused by unilateral lobectomy may offer important clues about the intra-cerebral source(s) of these effects.

In summary, the present findings confirm that unilateral temporal lobectomy is associated with abnormally small ERP modulations in a recognition memory task tapping long-term memory for words. The data suggest, however, that such abnormalities need not be more strongly associated with damage to the left than to the right temporal lobe. The data further suggest that whatever the processes reflected by old/new ERP effects in the latency range of the N400 component, they are unlikely to contribute significantly to verbal memory performance.

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REFERENCES

BABB TL, BROWN WJ (1987) Pathological findings in epilepsy. In: *Surgical Treatment of the Epilepsies.* Edited by J. Engel. New York: Raven Press, pp. 511–552.

BENTIN S, MOSCOVITCH M (1990) Psychophysiological indices of implicit memory performance. *Bulletin of the Psychonomic Society*, **28**, 346–352.

BENTIN S, PELED B-S (1990) The contribution of task-related factors to ERP repetition effects at short and long lags. *Memory and Cognition*, **18**, 359–366.

FALCONER MA (1971) Anterior temporal lobectomy for epilepsy. In: *Operative Surgery*, Volume 14. Second edition. Edited by C. Rob and R. Smith. London: Butterworths, pp. 142–149.

FRIEDMAN D (1990) ERPs during continuous recognition memory for words. *Biological Psychology*, **30**, 61–87.

HALGREN E, SMITH ME (1987) Cognitive evoked potentials as modulatory processes in human memory formation and retrieval. *Human Neurobiology*, **6**, 129–139.

HEIT G, SMITH ME, HALGREN E (1990) Neuronal activity in the human medial temporal lobe during recognition memory. *Brain*, **113**, 1093–1112.

JACOBY LL, DALLAS M (1981) On the relationship between autobiographical memory and perceptual learning *Journal of Experimental Psychology: General*, **110**, 306–340.

JENNINGS JR, WOOD CC (1976) The epsilon-adjustment procedure for repeated-measures analyses of variance. *Psychophysiology*, **13**, 277–278.

JOHNSON R (1988) Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. *Brain*, **111**, 1517–1529.

JOHNSON R, PFEFFERBAUM A, KOPELL BS (1985) P300 and long-term memory: latency predicts recognition performance. *Psychophysiology*, **22**, 497–507.

JOHNSON R, FEDIO P (1986) P300 activity in patients following unilateral temporal lobectomy: a preliminary report. *Electroencephalography and Clinical Neurophysiology*, Supplement 38, 552–554.

KARIS D, FABIANI M, DONCHIN E (1984) 'P300' and memory: individual differences in the von Restorff effect. *Cognitive Psychology*, **16**, 177–216.

KNIGHT RT, SCABINI D, WOODS DL, CLAYWORTH CC (1989) Contributions of temporal-parietal junction to the human auditory P3. *Brain Research, Amsterdam*, **502**, 109–116.

KUTAS M, HILLYARD SA, VOLPE BT, GAZZANIGA MS (1990) Late positive event-related potentials after commissural section in humans. *Journal of Cognitive Neuroscience*, **2**, 258–271.

NAGY ME, RUGG MD (1989) Modulation of event-related potentials by work repetition: the effects of inter-item lag. *Psychophysiology*, **26**, 431–436.

NEVILLE HJ, KUTAS M, CHESNEY G, SCHMIDT AL (1986) Event-related brain potentials during initial encoding and recognition memory of congruous and incongruous words. *Journal of Memory and Language*, **25**, 75–92.

POTTER DD, PICKLES CD, ROBERTS RC, RUGG MD (1991) The effects of scopolamine on event-related potentials in a continuous recognition memory task. *Psychophysiology.* In press.

RUGG MD (1990) Event-related brain potentials dissociate repetition effects of high- and low-frequency words. *Memory and Cognition*, **18**, 367–379.

RUGG MD, FURDA J, LORIST M (1988) The effects of task on the modulation of event-related potentials by word repetition. *Psychophysiology*, **25**, 55–63.

RUGG MD, NAGY ME (1989) Event-related potentials and recognition memory for words. *Electroencephalography and Clinical Neurophysiology*, **72**, 395–406.

RUGG MD, PICKLES CD, POTTER DD, ROBERTS RC (1991) Normal P300 following extensive damage to the left medial temporal lobe. *Journal of Neurology, Neurosurgery, and Psychiatry*, **54**, 217–222.

SMITH ME, STAPLETON JM, HALGREN E (1986) Human medial temporal lobe potentials evoked in memory and language tasks. *Electroencephalography and Clinical Neurophysiology*, **63**, 145–159.

SMITH ME, HALGREN E (1989) Dissociation of recognition memory components following temporal lobe lesions. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, **15**, 50–60

SMITH ML (1989) Memory disorders associated with temporal lobe lesions. In: *Handbook of Neuropsychology*, Volume 3. Edited by L. Squire. Amsterdam: Elsevier, pp. 91–106.

SNODGRASS JG, CORWIN J (1988) Pragmatics of measuring recognition memory: applications to dementia and amnesia. *Journal of Experimental Psychology: General*, **117**, 34–50.

STAPLETON JM, HALGREN E, MORENO KA (1987) Endogenous potentials after anterior temporal lobectomy. *Neuropsychologia*, **25**, 549–557.

STEPHENSON WA, GIBBS FA (1951) A balanced non-cephalic reference electrode. *Electroencephalography and Clinical Neurophysiology*, **3**, 237–240.

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INTRAHEMISPHERIC AND INTERHEMISPHERIC SPREAD OF CEREBRAL CORTICAL MYOCLONIC ACTIVITY AND ITS RELEVANCE TO EPILEPSY

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SUMMARY

Nine patients with cortical myoclonus (due to various pathologies), in whom movement of one limb induced bilateral limb jerks, were investigated. Three of these patients also had bilateral cortical reflex myoclonus when one limb was subjected to an electrical stimulus. The relative latencies to onset of electromyogram (EMG) activity in various ipsilateral and contralateral muscles in action and reflex jerks were studied.

Bilateral reflex and action jerks induced by unilateral electrical stimuli or limb movement were not synchronous. EMG activity was usually recorded in the muscles of the stimulated or moved limb, before being recorded in the homologous muscles of the contralateral limb. It is proposed that this difference in relative latency between homologous muscles represents the interhemispheric delay due to the transcallosal spread of excitation from one sensorimotor cortex to the opposite cerebral cortex.

The relative latencies of muscles on the same side of the body reflected not only the differences in efferent delays from the motor cortex via spinal cord and peripheral nerves, but also delays due to the spread of myoclonic activity within the sensorimotor cortex itself This intrahemispheric spread followed a grossly somatotopic pattern. It is suggested that this spread involves cortico-cortical pathways. The additional delay due to spread of activity from hand to leg area of the sensorimotor cortex was about 10 ms in the first active hemisphere, in both generalized reflex and action jerks. The delays due to somatotopic spread of activity in the opposite later activated hemisphere were shorter.

The tendency for spread of excitation through callosal and cortico-cortical pathways is an additional pathophysiological abnormality in some patients with cortical myoclonus, and may be important in the generalization of seizures seen in these patients.

INTRODUCTION

Cortical myoclonus is thought to involve the sensorimotor cortex and rapidly conducting pyramidal pathways (Kugelberg and Widén, 1954; Lhermitte *et al.*, 1971; Pagni *et al.*, 1971; Chauvel *et al.*, 1978; Hallett *et al.*, 1979). Focal stimulation of the sensorimotor cortex elicits a focal movement (Penfield and Boldrey, 1937). Cortical reflex and action myoclonus frequently is described as being focal or multifocal in its distribution (Hallett *et al.*, 1979; Obeso *et al.*, 1985). However, in their original report of post-anoxic cortical action myoclonus, Lance and Adams (1963) noted that generalized, as well as multifocal, action jerks could occur. This observation has since been reinforced by the studies of Thompson *et al.* (1989). In addition, the presence of bilateral C reflexes (elicited by unilateral electrical stimulation of a peripheral nerve) has been reported in some patients with cortical reflex myoclonus (Shibasaki *et al.*, 1978; Wilkins *et al.*, 1984). Little is

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known about the pathophysiological mechanisms underlying the spread of cortical excitation in these more extensive myoclonic jerks. Given the close links between the processes involved in cortical myoclonus and those leading to epilepsy (Obeso *et al.*, 1985), the same mechanisms of spread of cortical excitation may also be important in some forms of seizure generalization.

Over the last 2 yrs we have studied 25 patients with cortical myoclonus (as judged by the presence of a time-locked cortical correlate in the EEG activity preceding action jerks with a short latency, and in some, a pathologically enlarged cortical SEP). All the patients had either multifocal action or reflex myoclonus or a combination of the two. In addition, 9 of these patients had more extensive action or reflex jerks, which clinically were frequently bilateral and apparently synchronous. We investigated the pathophysiological mechanisms underlying the more extensive myoclonic jerks in these 9 patients by analysing the relative latency of EMG activity in different muscles. We conclude that generalized myoclonic jerks induced by unilateral peripheral stimulation or limb movement are due to the relatively rapid spread of activity from an initial focus in one sensorimotor cortex to other ipsilateral sensorimotor cortical areas through cortico-cortical pathways, and to the opposite sensorimotor cortex through the corpus callosum. This spread of excitation follows the somatotopic organization of the sensorimotor cortex and its callosal projections.

METHODS

Details of the 9 patients with cortical myoclonus and bilateral action or reflex jerks are presented in Table 1. All 9 patients had generalized seizures in addition to their myoclonus. Patients gave their informed consent to the neurophysiological studies, which included polymyography, back-averaging of the EEG activity preceding jerks and somatosensory evoked potentials (SEPs). SEPs were recorded following stimulation of the median nerve at the wrist with a constant voltage rectangular pulse of 0.2 ms duration at intensities just above motor threshold. SEPs were the average of 512 stimuli. Their amplitude was measured from the first major cortical positive peak following the stimulus (conventionally known as the P_{25}, here termed P_1) to the second major negative peak (the N_{33}, here termed N_2). The EEG was recorded from silver/silver chloride electrodes fixed to the scalp with collodion and referred to linked ear-lobe electrodes for SEPs. The signals were band pass filtered at 3 kHz with a time constant of 1.0 s. The sampling rate was 3000 Hz per channel. The EEG recording sites were standard positions of the 10–20 systems with additional electrodes used between these sites for the localization of focal cerebral activity, as necessary. A bipolar electrode montage (*see* Fig. 3) was used for back-averaging the EEG activity occurring before action jerks. In the EEG records shown positivity is downward.

EMG recordings were made using bipolar silver/silver chloride electrodes placed 2 cm apart longitudinally over the muscle bellies. The relative latencies to onset of EMG activity in reflex and action jerks were measured from single trials. When collecting bilateral action jerks the patient sat supported comfortably, while moving one arm to command. The other limbs were relaxed. EMG activity in the relaxed arm was used to trigger the collection of EEG and EMG activity in bilateral jerks. The bilaterality of the jerks was later confirmed by visual inspection of the records.

The latency differences between muscles following magnetic stimulation of the motor cortex were calculated from Thompson (1991).

RESULTS

Cortical reflex myoclonus

Interhemispheric delays in bilateral reflex jerks. Three (Cases 3, 5 and 6) of the 9 patients had cortical reflex myoclonus in response to peripheral somatosensory stimuli,

TABLE 1 CLINICAL DETAILS

Case	Age	Diagnosis	*P_1 N_2 following electrical stimulation median nerve at wrist* Right (μV)	Left (μV)	*Reflex jerks to electrical stimulation median nerve*	*Time-locked cortical correlate preceding action jerks*	*Multifocal action jerks*	*Generalized action jerks*
1	75	Post-anoxic encephalopathy	1.5	N/A	–	+	+	–
2	43	Huntington's disease	2.6	1.7	–	+	+	–
3	25	Progressive myoclonic ataxia*	18.0	9.3	+	+	+	+
4	71	Post-anoxic encephalopathy	0.5	0.5	–	+	+	–
5	48	Myoclonus in association with coeliac disease	N/A	50.0	+	+	+	–
6	32	Progressive myoclonic ataxia*	7.5	16.5	+	+	+	–
7	25	Progressive myoclonic ataxia*	2.3	2.2	–	+	+	+
8	37	Progressive myoclonic ataxia*	–	–	(+)	+	+	+
9	50	Post-anoxic encephalopathy	2.7	N/A	–	+	+	+

All 9 cases had evidence of cortical action myoclonus with a time-locked cortical correlate recorded in the back-averaged EEG activity preceding action jerks at short latency. In addition, Cases 3, 5 and 6 had cortical reflex myoclonus with giant cortical SEPs. In Case 8 the P_1 N_2 waveform was absent, and reflex responses were of long latency (following a tap to the right elbow reflex EMG activity was recorded in biceps at about 80 ms) The origin of the reflex myoclonus in this patient could not be established, so her reflex jerks were not studied further. In 14 healthy control subjects, aged 18 to 60, the mean P_1 N_2 amplitude was 1.8 μV (range 0.4–3.4 μV). N/A denotes not available. *No underlying cause found, despite full investigation.

in addition to their action-induced myoclonus. In all 3, stimulation of the median nerve at the wrist on one side of the body elicited bilateral jerks in both arms. Although the bilateral jerks seemed synchronous clinically, polymyography revealed a consistent delay between homologous muscles on the two sides of the body. Reflex EMG activity was always recorded earlier in the muscles of the stimulated side. In the example illustrated in Fig. 1, the average unrectified surface EMG records show that the jerk elicited by stimulation of the left median nerve occurred about 10 ms earlier in the left forearm extensors than in those on the right. Inter-side latency differences in the bilateral reflex jerks induced by unilateral peripheral stimuli were similar in all 3 patients (Table 2).

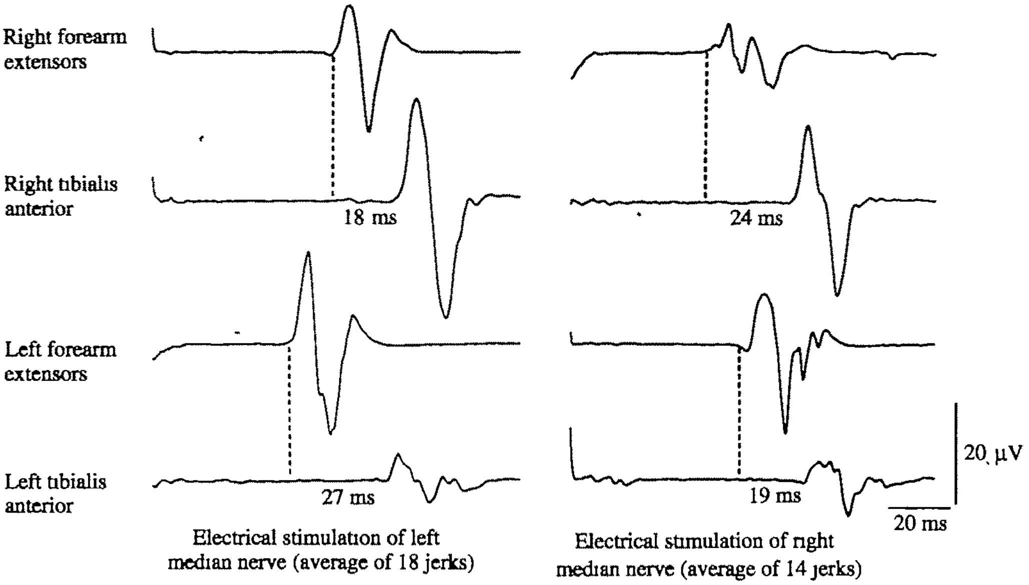

FIG. 1. The generalized reflex response to electrical stimulation of the median nerve at the wrist in *Case 3* The records of the reflex EMG activity elicited by electrical stimulation of the left and right median nerves represent the average of the unrectified EMG activity in 18 and 14 reflex jerks, respectively. Reflex EMG activity in the forearm extensor muscles of the stimulated arm precedes that recorded in the forearm extensor muscles of the opposite arm, suggesting a delay in activation of the sensorimotor cortex ipsilateral to the stimulated arm. In addition, the difference in latency to onset of reflex EMG activity between the forearm extensor muscles and tibialis anterior on the side of stimulation exceeds that recorded on the opposite side of the body as shown. The relatively excessive latency of tibialis anterior with stimulation of the ipsilateral median nerve is reversed with stimulation of the contralateral median nerve This indicates that the relative excessive latency of tibialis anterior, on the side of stimulation of the median nerve, is not due to a delay in the pyramidal pathways to this leg. It is suggested that the extra delay in onset of reflex EMG activity in tibialis anterior on the side of stimulation is due to the delay for spread of excitation from the hand area to the leg area of the contralateral sensorimotor cortex. This delay is less in the sensorimotor cortex ipsilateral to the side of the stimulated limb

The inter-side latency differences in the reflex jerks following electrical stimulation of the median nerve at the wrist were paralleled by differences in the SEPs recorded over each hemisphere. The giant positive (P_1) wave recorded over the hemisphere contralateral to the side of stimulation was followed 9.4 to 17.6 ms later by an ipsilateral

TABLE 2 INTERHEMISPHERIC DELAY IN BILATERAL REFLEX JERKS

	Electrical stimulation of left median nerve at wrist	*Electrical stimulation of right median nerve at wrist*	*Electrical stimulation of left posterior tibial nerve at ankle*
Case	*Excess latency (±SEM) of right relative to left forearm extensors (ms)*	*Excess latency (±SEM) of left relative to right forearm extensors (ms)*	*Excess latency (±SEM) of right relative to left tibialis anterior (ms)*
3	10.1±0.5 (n = 21)	10.3±0.4 (n = 32)	11.0±0.5 (n = 25)
5	11.4±0.5 (n = 14)	11.2±0.3 (n = 49)	–
6	13.4±0.7 (n = 6)	15.6±0.7 (n = 15)	–

Latencies were measured to the onset of EMG activity.

enlarged P_1 wave in the cortical SEP. Both the contralateral and ipsilateral P_1 waves preceded the reflex EMG activity in the opposite forearms by about 16 ms. This is the approximate latency of the EMG activity in the forearm muscles following magnetic stimulation of the motor cortex. As suggested originally by Shibasaki *et al.* (1978), the inter-side difference in both the latency of the evoked potential and the accompanying reflex response may represent the delay for transcallosal spread of excitation from one sensorimotor cortex to the other.

Somatotopic spread in generalized reflex jerks. In Cases 5 and 6 the bilateral reflex jerks only involved the arms, but in Case 3 the bilateral reflex jerks were generalized. In this patient stimulation of the median or tibial nerves on one side elicited a bilateral jerk in both arms and legs. The relative latencies of muscles in these generalized reflex jerks suggested that myoclonic activity not only spread transcallosally to the non-stimulated hemisphere, but also spread intrahemispherically along the somatotopic body map of the sensorimotor cortex. Evidence for this is illustrated in Fig. 1 and summarized in Table 3. Following electrical stimulation of the left median nerve at the wrist the difference in reflex latency between left forearm extensors and tibialis anterior was 27.2 (±0.6) ms. The difference in latency between the forearm extensors and tibialis anterior following magnetic stimulation of the motor cortex is about 16 ms. Given that cortical reflex myoclonus is believed to involve rapidly conducting corticospinal pathways (Kugelberg and Widén, 1954; Lhermitte *et al.*, 1971; Pagni *et al.*, 1971; Chauvel *et al.*, 1978; Hallett *et al.*, 1979) similar to those activated by magnetic stimulation of the motor cortex (Barker *et al.*, 1985; Hess *et al.*, 1987), the difference in the reflex latency between arm and leg ipsilateral to the side of stimulation was about 11 ms longer than expected.

The extra delay in latency of the left tibialis anterior relative to the left forearm muscles following stimulation of the left median nerve cannot be accounted for by a conduction delay in the rapidly conducting pyramidal pathways to the left leg. When the right median nerve at the wrist was stimulated, the difference in latency between the left forearm extensors and tibialis anterior was only 19.0 (±0.6) ms (only 3 ms longer than the difference expected following magnetic stimulation of the motor cortex). Instead, the extra delay on stimulation of the left median nerve at the wrist may represent the time necessary for spread of excitation from the 'stimulated' hand area to the leg area in the right sensorimotor cortex. (A similarly excessive difference in latency, 24.1±0.9 ms, was seen between the right forearm extensors and tibialis anterior when the right median nerve at the wrist was stimulated.)

If the extra 11 ms difference in latency between arm and leg muscles on the side of the median nerve stimulation is due to the extra time necessary for the spread of excitation from the hand area to the leg area in the contralateral hemisphere, then the difference in latency between arm and leg muscles following peripheral stimulation of the leg should be shorter than following magnetic stimulation of the motor cortex. This is because activation of arm muscles will take about 11 ms longer than leg muscles as spread now occurs from leg to arm area of the contralateral hemisphere. As predicted, when the left posterior tibial nerve at the ankle was electrically stimulated, the difference in the latency of the reflex response in left biceps and tibialis anterior was 7.1 ±0.5 ms (Table 3). This is about 11 ms shorter than the difference in latency between biceps and tibialis anterior following magnetic stimulation of the motor cortex.

TABLE 3 RELATIVE LATENCIES TO ONSET OF EMG ACTIVITY IN REFLEX JERKS IN CASE 3

	Latency difference ±SEM (ms)		
	Electrical stimulation of left median nerve at wrist	*Electrical stimulation of right median nerve at wrist*	*Magnetic stimulation of motor cortex**
Right tibialis anterior–right forearm extensors	18.5±0.6 (n = 18)	24.1±0.9 (n = 14)	16.0
Left tibialis anterior–left forearm extensors	27.2±0.6 (n = 18)	19.0±0.6 (n = 14)	16.0
	Electrical stimulation of left posterior tibial nerve at ankle		*Magnetic stimulation of motor cortex**
Right tibialis anterior–right biceps	13.2±0.9 (n = 14)		18.5
Left tibialis anterior–left biceps	7.1±0.5 (n = 29)		18.5

*Calculated from Thompson (1991).

The difference in reflex latencies between arm and leg muscles on the side of the body contralateral to the peripheral stimulus was closer to that predicted from magnetic stimulation of the motor cortex. However, it was still about 3 ms longer or shorter than predicted, following electrical stimulation of the contralateral median or posterior tibial nerves respectively (Table 3). This suggests that the delay due to spread of myoclonic activity between arm and hand areas is shorter in the ipsilateral hemisphere than in the hemisphere contralateral to the peripheral stimulus.

Cortical action myoclonus

Interhemispheric delays in bilateral action jerks. All the patients had multifocal action myoclonus, with jerks confined to the active limb. In addition, action jerks induced by the movement of one limb were often generalized, involving both arms and legs, in 4 patients (Cases 3, 7, 8 and 9). The remaining 5 patients had action jerks which often involved the arms bilaterally during voluntary movements of either arm. In these 5 patients the jerks recorded during voluntary movements of the legs were restricted to the active leg.

Although the clinical impression was that bilateral jerks induced by movement of one arm occurred synchronously in both arms, polymyography revealed that such bilateral jerks were not truly synchronous (Fig. 2). In most patients (Cases 1, 2, 3, 4, 6, 7 and 8), EMG activity was usually (but not always) recorded in the muscles of the active arm before being recorded in homologous muscles on the other, resting, side. (In Cases 5 and 9 EMG activity in the majority of bilateral jerks was recorded first in muscles of the left and right sides of the body respectively, regardless of which side was active at the time.) In those jerks in which EMG activity was recorded first in muscles of the left side of the body, the median difference in latency between the left and right forearm extensors or intrinsic hand muscles ranged from 3 to 10 ms between the 9 patients. Conversely, in those jerks in which EMG activity was recorded first in muscles of the right side of the body, the median difference in latency between the right and left forearm extensors or intrinsic hand muscles ranged from 3 to 8 ms.

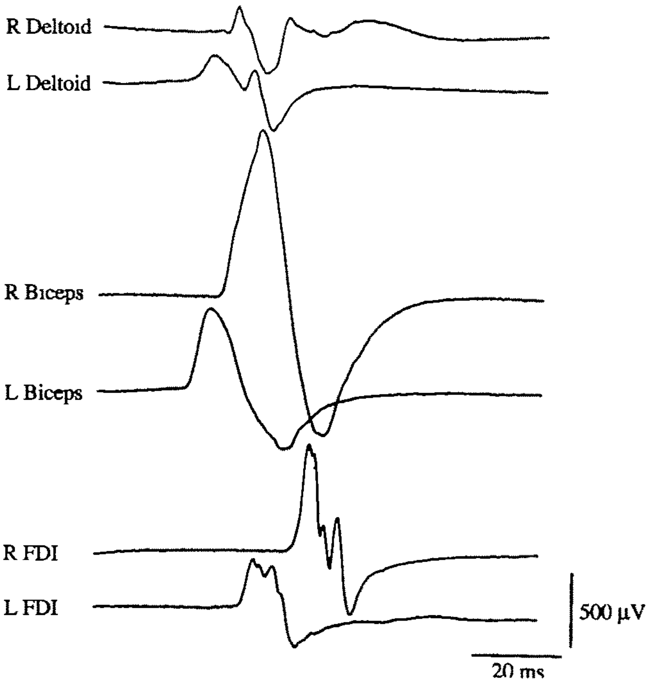

FIG. 2 A record of the unrectified EMG activity in a single bilateral action jerk induced by movement of the left arm in *Case 8*. EMG activity is recorded in left (L) before right (R) sided muscles

The latency of the EMG response following electrical stimulation of the motor cortex is shorter in active than resting muscles (Rothwell *et al.*, 1987). Day *et al.* (1987) have speculated on the mechanisms underlying this shortening of latency. It is unlikely, however, that similar mechanisms are responsible for the differences in latency between homologous muscle pairs in bilateral action jerks as EMG activity was often recorded first in the inactive limb (particularly in Cases 5 and 9). In addition, a delay was also apparent in the back-averaged EEG correlates recorded over the two cerebral hemispheres in the bilateral jerks induced by movement of one limb. Fig. 3 shows the back-averaged EEG activity preceding 33 generalized jerks in which EMG activity was recorded in muscles of the left arm before homologous muscles of the right arm in Case 8. The cortical correlate recorded over the right hemisphere preceded that recorded over the left hemisphere by about 8 ms. Similarly, the median difference in relative latency between left and right biceps was 7 ms in this patient.

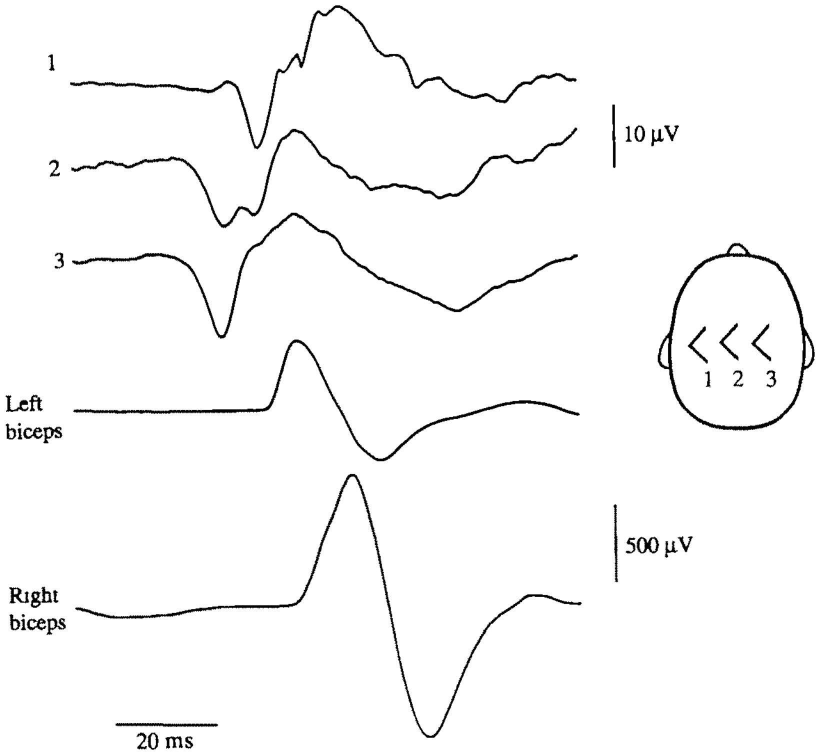

FIG 3 Back-averaged EEG activity preceding bilateral action jerks induced by voluntary movement of the left arm in *Case 8*. EMG activity is recorded in muscles of the left upper limb before those of the right upper limb The record is the average of 33 such jerks. A bipolar EEG electrode montage was used, with the frontal electrodes as reference The later onset of EMG activity in right biceps is reflected in the later onset of the cortical correlate recorded over the left sensorimotor cortex. This suggests that there is a delay between activation of the left and right sensorimotor cortices in bilateral action jerks.

Somatotopic spread in generalized action jerks. There are two possible explanations for the generalized action myoclonus induced by movement of one limb in Cases 3, 7, 8 and 9. First, generalized jerks might be the result of the simultaneous and synchronous activation of all of the right and left motor cortex. In this case, the latency differences between different muscles in the generalized action jerks would be fixed according to the efferent delays to these muscles from the cortex. (The latter can be estimated from the latencies of these muscles following magnetic stimulation of the motor cortex.)

The second possibility is that generalized action jerks might be the result of the spread of myoclonic activity within the sensorimotor cortex, as in the generalized reflex jerks induced by a peripheral stimulus in Case 3. In essence, myoclonic activity might spread through the cortex from a single focus, the location of which is not fixed, but could vary from jerk to jerk. Thus, the differences in relative latencies of muscles in the action jerks would reflect both the efferent delays to these muscles, as predicted by magnetic stimulation of the motor cortex, and additional delays due to spread of the myoclonic activity within the cerebral cortex. Such delays would vary with the site of origin of the myoclonic activity, and their pattern might be expected to reflect the known somatotopy of the sensorimotor cortex (Penfield and Boldrey, 1937). The way in which variation in the site of the cortical focus will change the latency difference between muscles is shown in Fig. 4. The model described in Fig. 4 applies to any given set of muscles. A specific example, illustrating the proposed effect of cortical spread on the relative latencies to onset of EMG activity in the first dorsal interrosseous (FDI), pectoralis major and tibialis anterior, is worked through in the legend to Fig. 5.

The relative latencies of muscles in the generalized action jerks occurring with voluntary movements of the arms and legs were recorded in Cases 3, 7, 8 and 9. The differences in relative latency between FDI and tibialis anterior, and between FDI and pectoralis major, were measured from single trials and plotted. The difference in relative latency between muscle pairs was measured on the side of the body from which the EMG activity in the action jerks was recorded first. In each case the latency differences did not cluster around the point predicted from the latencies of these muscles to magnetic stimulation of the major cortex, and therefore did not support the theory of synchronous activation of the whole motor cortex in generalized action jerks. Instead the relationship between the difference in relative latency of FDI and tibialis anterior, and that of FDI and pectoralis major was strikingly similar to that predicted if intracortical spread of myoclonic activity were to occur (Fig. 5).

In the model of cortical spread in generalized action jerks (illustrated and explained in Fig. 4), the maximum difference in latency between FDI and any other muscle is equal to the difference in efferent latencies between the two muscles plus the delay in spread from the hand area to the sensorimotor cortex representation of the second muscle. Similarly, the minimum difference in latency between FDI and any other muscle is equal to the difference in efferent latency minus the delay in spread from the hand area to the sensorimotor cortex representation of the second muscle. Thus the range of difference in latency between FDI and any other muscle approximates to twice the delay in spread from the hand area to the sensorimotor cortex representation of the second muscle. If cortical spread follows the known somatotopy of the sensorimotor cortex (Penfield and Boldrey, 1937), then the range of values for the difference between FDI and more proximal muscles should become progressively less as the delay in spread from the hand area to the motor cortex representations of these more proximal muscles shortens. The ranges in the differences in latency between FDI and leg, shoulder and upper arm muscles

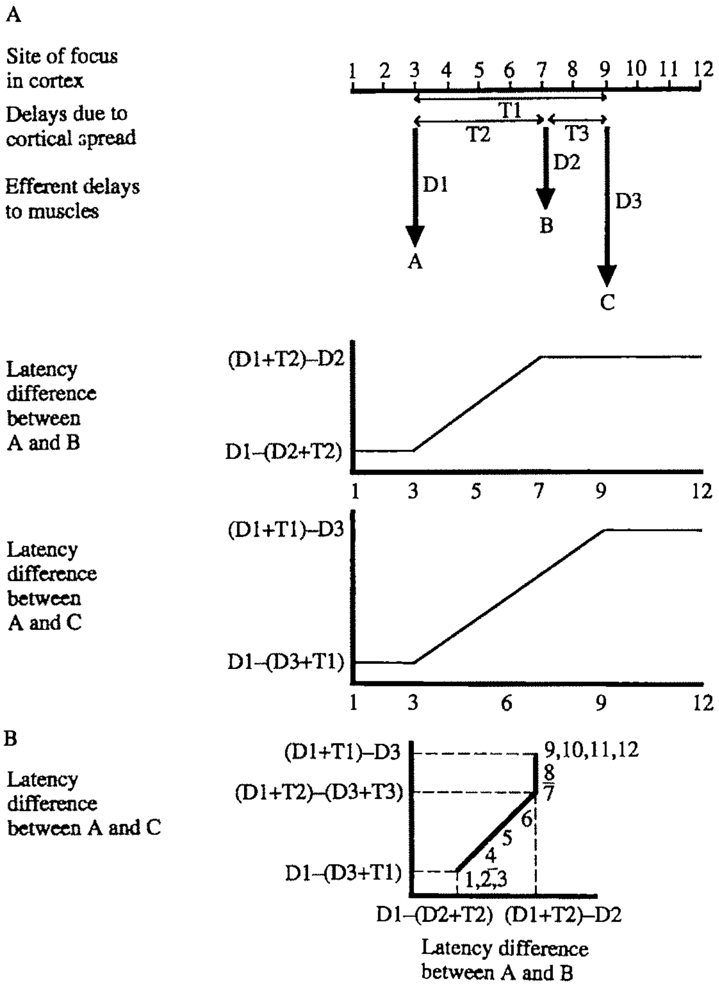

FIG 4. A illustrates the way in which the latency difference between a pair of muscles varies with the site of the myoclonic focus within the cortex, assuming that excitation then spreads along the cortex from this focus. The site of the myoclonic focus may vary between action jerks as different movements are made D1, D2 and D3 represent the efferent delays to muscles A, B and C respectively T1, T2 and T3 are the delays due to cortical spread between the cortical representations of muscles A and C, A and B, and B and C, respectively. It is apparent from this figure that the range in possible latency differences between A and B represents twice T2. This is because the latency difference between muscles A and B is greatest when myoclonic activity starts at the cortical representation of B (i e at point 7 in the cortex), and is then equal to (D1+T2)−D2, which is equivalent to (D1−D2)+T2 The latency difference between muscles A and B is smallest when myoclonic activity starts at the cortical representation of A (i e at point 3 in the cortex), and is then equal to D1−(D2+T2), which is equivalent to (D1−D2)−T2. Thus, the range in possible latency differences between A and B is [(D1−D2)+T2]−[(D1−D2)−T2], which equals 2×T2. Similarly, the range in possible latency differences between A and C represents twice T1. B then shows how the latency differences between two muscle pairs will be related if generalized action jerks are the result of the intracortical spread of myoclonic activity The numbered points refer to the site of origin of the myoclonic activity along the cortex (as shown in A)

were therefore measured in Cases 3, 7, 8 and 9. The means of the ranges in latency differences between FDI and tibialis anterior, FDI and pectoralis major, and FDI and biceps were 20.6, 15.0 and 9.0 ms, respectively. The estimated mean delays (*see* legend

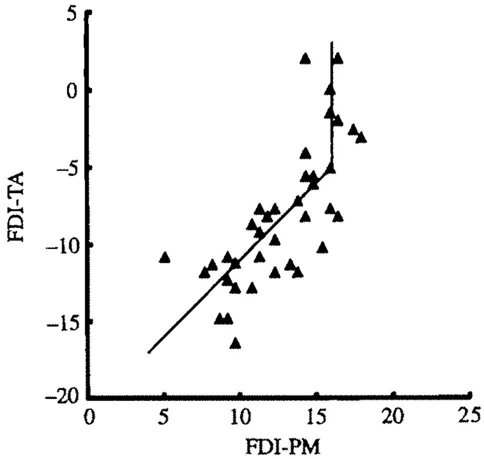

FIG 5 The difference in relative latency in generalized action jerks (n = 40) between the first dorsal interosseous (FDI) and tibialis anterior (TA) has been plotted against that between FDI and pectoralis major (PM) in Case 7. The jerks were elicited by the voluntary movement of each limb in turn The differences in latency have been measured from the side of the body from which EMG activity is recorded first (and therefore reflect activity in the first active or 'leading' cerebral hemisphere) The differences in latency do not cluster around a single point as would be expected if the whole motor cortex were synchronously activated Instead, they approximate to the relationship predicted if the relative latencies of muscles were determined by both efferent delays from the motor cortex and intrahemispheric delays due to the spread of myoclonic activity. The latter relationship is illustrated by the solid line. This predicted relationship assumes that the delay due to spread from hand to leg area of the sensorimotor cortex is about 10 ms (as suggested by the generalized reflex jerks in *Case 3*), and assumes a delay due to spread from hand to chest area of about 6 ms (allowing for the disproportionate cortical representation of the hand and arm). If the efferent delays are similar to those seen after magnetic stimulation of the motor cortex (Thompson, 1991), then the relative latencies of FDI, PM and TA are about 22 ms, (12+6) ms and (29+10) ms, respectively, for jerks in which myoclonic activity starts in the hand area of the sensorimotor cortex Therefore, the difference in latency between FDI and TA is about −17 ms, and that between FDI and PM is about 4 ms. For those jerks in which myoclonic activity begins in the leg area of the sensorimotor cortex the relative latencies of FDI, PM and TA are about (22+10) ms, (12+4) ms and 29 ms, respectively. The difference in latency between FDI and TA is then about 3 ms. At the same time the difference in latency between FDI and PM is about 16 ms. Finally, for those jerks in which myoclonic activity begins in the chest area of the sensorimotor cortex the relative latencies of FDI, PM and TA are about (22+6) ms, 12 ms and (29+4) ms, respectively. The difference in latency between FDI and TA is then about −5 ms, and that between FDI and PM is about 16 ms.

to Fig. 4) for cortical spread between the hand area and cortical representations of the leg, shoulder and upper arm were 10.3, 7.5 and 4.5 ms, respectively, indicating that the spread of myoclonic activity followed a somatotopic pattern.

The above results pertain to the side of the body in which EMG activity is recorded first in generalized action jerks induced by movement of one limb. It is suggested, therefore, that they reflect events in the leading hemisphere (although this hemisphere need not always be contralateral to the active hand).

The relative latencies of muscles in the generalized reflex jerks in Case 3 suggested that delays due to cortical spread were also present in the later active hemisphere, but that these delays were shorter. The possibility of cortical spread in the later active hemisphere was therefore investigated in the generalized action jerks. It was suggested above that activity in this hemisphere is delayed because it is activated by the leading hemisphere through callosal pathways. If interhemispheric connectivity were homotopically arranged, then myoclonic activity in the later active hemisphere will start at, and spread from, the same site as the leading hemisphere. In each generalized jerk, therefore, the latency difference between two muscles on one side of the body should be the same as on the other side. The initial focus of cortical myoclonic activity will vary in site between jerks so that the latency differences between muscles on each side of the body should vary in parallel. In other words, if interhemispheric connectivity is homotopically arranged, then, for a pair of muscles involved in a number of jerks, the latency difference on the leading side should be linearly correlated with the latency difference on the later active side, and the slope of the relationship should be unity.

The latency differences between tibialis anterior and FDI were measured in the 4 patients with generalized action jerks and a significant linear correlation was found between the latency differences on the two sides of the body (correlation coefficients 0.673, 0.666, 0.710 and 0.677 in Cases 3, 7, 8 and 9, respectively; $P < 0.001$ in each case). However, the regression coefficient was always less than 1 (0.790, 0.601, 0.721 and 0.481 in Cases 3, 7, 8 and 9, respectively), implying that the delays due to spread of myoclonic activity in the later activated hemisphere were shorter than in the 'leading' hemisphere (Fig. 6).

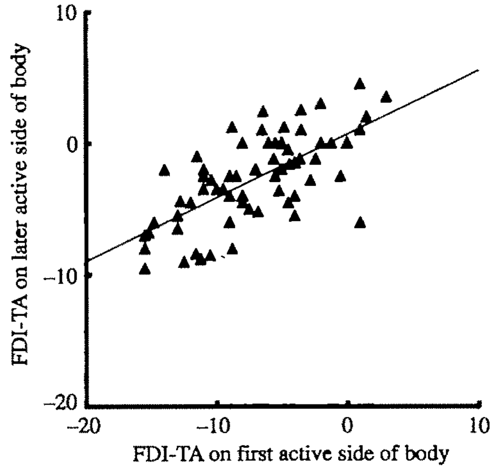

FIG. 6. The difference in the relative latency to onset of EMG activity between tibialis anterior (TA) and first dorsal interosseous (FDI) is compared for the two sides of the body in the generalized action jerks (n = 70) in *Case 9*. The difference in latency between TA and FDI on the side of the body from which EMG activity is recorded first has been plotted against that measured on the side of the body from which activity in homologous muscles is delayed, for each generalized action jerk. Jerks were elicited by the voluntary movement of each limb in turn There is a significant positive correlation ($r = 0.677$, $P < 0.001$) between these two variables, suggesting that spread of myoclonic activity occurs in both cerebral hemispheres (Regression coefficient = 0 481.)

DISCUSSION

Cortical myoclonus is not always focal or multifocal. The 9 patients with cortical myoclonus studied here all had bilateral action jerks, and 3 had bilateral reflex jerks. In addition, the pattern of muscle recruitment during the action and reflex myoclonus varied, and was not simply a function of the central and peripheral efferent delays to individual muscles. Instead the pattern of muscle recruitment was complicated by additional delays for the spread of myoclonic activity within the sensorimotor cortex and across the corpus callosum.

Interhemispheric excitation

Bilateral reflex and action jerks induced by a unilateral peripheral stimulus, or movement of one limb, were not synchronous. Homologous muscles on the two sides of the body showed differences in relative latencies of 10.1 to 15.6 ms in reflex jerks, and 3.0 to 10.0 ms in action jerks. Assuming that the efferent delays are similar from the two sensorimotor cortices, the differences in latency between homologous muscles on the two sides of the body suggests a delay in the spread of activity to the other hemisphere. This interpretation is supported by the difference in the relative latency of the enlarged P_1 component of the cortical SEP and the cortical correlate of the back-averaged EEG. Both were delayed over the hemisphere contralateral to the delayed reflex or action response. The presence of delayed cortical components of the SEP over the hemisphere ipsilateral to the stimulus has been previously reported (Shibasaki *et al.*, 1978, 1985; Wilkins *et al.*, 1984).

Anatomical techniques have established that the sensorimotor cortices project to one another through the corpus callosum (Jones and Powell, 1969; Pandya and Vignolo, 1969; Karol and Pandya, 1971; Shanks *et al.*, 1975). Experimentally, electrical stimulation of the sensorimotor cortex can give rise to activity in the pyramidal tract from the contralateral hemisphere (Purpura and Girado, 1959). Pyramidal tract activity, and even movement, can also be elicited by direct electrical stimulation of the corpus callosum (Mott and Schaefer, 1890; Purpura and Girado, 1959; Spidalieri *et al.*, 1986). Shibasaki *et al.* (1978) have already intimated that the C reflex in muscles contralateral to a peripheral stimulus may involve the transcallosal spread of excitation in cortical reflex myoclonus.

The delay between activation of the two hemispheres in the bilateral reflex and action jerks induced by unilateral peripheral stimuli or movement, may, therefore, be due to the transcallosal excitation of one hemisphere by the other. However, the interhemispheric delay in bilateral action jerks was very short (range 3 to 10 ms). The minimum latency of the transcallosal evoked response recorded in man is 8.8 ms (Cracco *et al.*, 1989). Cracco *et al.* (1989), on the basis of the diameter of human callosal axons, argued that 7.8 ms represents the minimum delay over the callosal conduction pathway in man. These authors underestimated the conduction velocity/axon diameter ratio in their calculations (Waxman and Bennett, 1972; Paintal, 1978). In the cat excitation of the contralateral cortex precedes the transcallosal evoked response (Purpura and Girado, 1959), and Ferbert *et al.* (1990), during their investigation of the transcallosally mediated inhibition following motor cortex stimulation in man, found some evidence to suggest the existence of transcallosal excitation at a latency of 4 ms. Finally, our calculation of the interhemispheric delay in action jerks is likely to be an underestimate of the true interhemispheric delay. The calculation involved measuring the difference in latency between forearm or intrinsic hand muscles between the two sides of the body during voluntary movements of one arm. In some of the measured action jerks, however, myoclonic activity may not have begun in the cortical representation of the distal arm.

In such jerks, spread to involve the cortical representation of the distal arm will have been more rapid in the later active hemisphere than in the leading hemisphere, leading to an underestimate of the true interhemispheric delay.

If the interhemispheric delay seen in cortical reflex and action myoclonus is not due to the transcallosal excitation of the second hemisphere, then the subcortical structures which might be involved in the transfer of activity from one to another side are unclear. Milhorat (1967) suggested that the mesial thalamic nuclei may play a central role in the genesis of myoclonic discharges, but these thalamic nuclei connect little, if at all, with their contralateral counterparts (Jones, 1985). The striatum has been involved in some experimental models of cortical myoclonus (Jenner *et al.*, 1981; Patel and Slater, 1987), and it is conceivable that excitation might travel from one motor cortex via projections to the contralateral striatum (Künzle, 1975; Collins, 1978*a*), and hence, via projections to the globus pallidus or substantia nigra, to the thalamus and motor cortex of the opposite hemisphere (Brodal, 1981; Patel and Slater, 1987). However, such an indirect and slowly conducting circuit would probably take too long to account for the brief interhemispheric delays seen in bilateral cortical myoclonus.

Pathological changes in the cerebellum are common in the Ramsay Hunt syndrome (Hunt, 1921; Bird and Shaw, 1978) and anoxic encephalopathy (Hauw *et al.*, 1986), raising the possibility that cerebellar dysfunction is important in the pathophysiology of cortical myoclonus. The brief interhemispheric delays seen in bilateral cortical myoclonus are unlikely to represent the delay for activation of the contralateral hemisphere through a lengthy cortico-cerebello-cortical loop (Brodal, 1981). Alternatively, it has been suggested that action myoclonus may be due to cerebellar discharge (Lance and Adams, 1963) firing both motor cortices via the ventrolateral nucleus of the thalamus, and dentate and interpositus nuclei (Brodal, 1981). Delays in the activation of muscles on the two sides might, then, reflect conduction delays in cerebellar commissural pathways. However, Lhermitte *et al.* (1971) only recorded spikes in the ventrolateral nucleus of the thalamus following discharge of the motor cortex in a patient with action myoclonus.

In conclusion, the most parsimonious explanation for the interhemispheric delay seen in bilateral cortical myoclonus is that it represents delays in established transcallosal pathways. Abnormal interhemispheric spread of myoclonic activity is not seen in all patients with cortical reflex or action myoclonus. In many patients the cortical myoclonus remains multifocal, so that only the stimulated or active limb is involved in the myoclonic response. This suggests that the interhemispheric spread of excitation represents an additional and separate pathophysiological deficit in some patients with cortical myoclonus. At the same time this abnormal interhemispheric excitation may underlie the generalized seizures occurring in many patients with cortical myoclonus (and present in Cases 1 to 9). Bilateralization of seizures through the corpus callosum has already been suggested in certain forms of epilepsy in man, based on temporal differences between the two hemispheres (Brazier, 1972; Gotman, 1981, 1983), and the results of anterior corpus callosotomy (Van Wagenen and Herren, 1940; Wilson *et al.*, 1982). The integrity of callosal connections is critical for seizure generalization in cats (Wada and Sato 1975; Wada *et al.*, 1982), monkeys (Marcus and Watson, 1968) and the photosensitive baboon, *Papio papio* (Wada and Mizoguchi, 1984; Wada and Komai, 1985). Furthermore, comparative studies between non-epileptic rhesus monkeys and epileptic baboons of the effect of callosal bisection on amygdaloid kindling suggest that callosal dysfunction may be important in the seizure predisposition of *Papio papio* (Wada and Mizoguchi, 1984; Wada and Komai, 1985).

Intrahemispheric spread of myoclonic activity

The generalized cortical reflex and action myoclonus studied here was not the result of the simultaneous activation of the whole of the motor cortex of both hemispheres. The relative latencies of muscles on each side of the body reflected not only the differences in efferent delays from the motor cortex, but also delays due to the intrahemispheric spread of activity. This intrahemispheric spread follows a grossly somatotopic pattern; the delay due to intrahemispheric spread from the hand area to the leg area exceeds that due to spread from the hand area to the chest area, which in turn exceeds that due to spread from the hand area to the proximal arm area. The delay due to spread from hand area to chest area was about three-quarters of the total delay due to spread from the hand area to leg area, suggesting that the representation of the upper limb is disproportionately large. The most parsimonious explanation for this intrahemispheric somatotopic spread of activity in cortical myoclonus is that it occurs at the sensorimotor cortex, where Penfield and Boldrey (1937) have identified somatotopic body representations in man, disproportionate in their representation of the face and upper limb. Somatotopic spread of cortical activity has been recorded in animals under chloralose anaesthesia following focal stimulation of the cerebral cortex (Erickson, 1940; Rosenblueth and Cannon, 1942). An alternative explanation is that spread occurs within a subcortical structure with somatotopic arrangement before reaching the cortex, where the myoclonic discharge is generated.

It is important to note that the method used here only indicates that intrahemispheric spread occurs, and that this follows a grossly somatotopic pattern. This last conclusion makes the assumption that spread between the areas of the sensorimotor cortex representing different body parts occurs at approximately the same velocity; only then can differing delays be interpreted as representing different intrahemispheric distances. The method, based on the varying relationships of relative muscle latencies, cannot shed any light on the finer details of central representations of the body. In particular this investigation does not distinguish between the existence of a single somatotopic representation of body movements within each motor area, as implied by Woolsey *et al.* (Woolsey, 1958, 1964), or the existence of a mosaic of multiple representations of movements that tend to be somatotopically arranged (Gould *et al.*, 1986).

Analysis of the relative muscle latencies in both reflex and action jerks suggests that excitation takes about 10 ms to reach the leg area from the hand area in the first active hemisphere. If this spread occurs in the sensorimotor cortex then it is relatively rapid. The lowest threshold points for electrical stimulation of the leg and hand areas of the motor cortex lie 7 cm apart on the scalp (Rothwell *et al.*, 1987). Assuming that this represents an approximately similar distance at the cortical surface, then the velocity of spread across the cortical surface is about 7 $m \cdot s^{-1}$. This is faster than the maximum conduction velocity of unmyelinated axons in the peripheral nervous system (Gasser, 1950), and suggests conduction in myelinated cortico-cortical pathways.

The extent of horizontal cortical connectivity has only recently been fully recognized. Pyramidal cells in the monkey sensorimotor cortex give rise to an extensive system of horizontal running long axons and axon collaterals (Vogt and Pandya, 1978; DeFelipe *et al.*, 1986). Pyramidal cells are excitatory (Kisvárdy *et al.*, 1986; Gabbott *et al.*, 1987; Kang *et al.*, 1988). Many pyramidal cell axon collaterals run intracortically, where their conduction velocity is only about 1.1 $\mathrm{m \cdot s^{-1}}$ (Kang *et al.*, 1988). However, other pyramidal cell axons and axon collaterals run subcortically (Jones *et al.*, 1978; DeFelipe *et al.*, 1986). These long myelinated axons and axon collaterals are 1 to 5 μm in diameter (DeFelipe *et al.*, 1986), suggesting a conduction velocity of 4.5 to 22.5 $\mathrm{m \cdot s^{-1}}$ (Waxman and Bennett, 1972; Paintal, 1978). It is suggested that the intrahemispheric somatotopic spread of myoclonic activity involves propagation through myelinated axons and axon collaterals of excitatory cortical pyramidal cells found in normal cerebral cortex.

The estimated delay for the spread of excitation from the hand area to the leg area was shorter in the later activated hemisphere, than in the leading hemisphere. There are two possible explanations for this. First, anatomical studies in primates indicate that the transcallosal pathways interconnecting the sensorimotor cortices are not strictly homotopic (Pandya and Vignolo, 1969; Shanks *et al.*, 1975; Jenny, 1979), but project also to regions of the contralateral cortex which represent adjacent segments of the body. This would mean that myoclonic activity starting focally in the sensorimotor cortex of one hemisphere will be transferred to more extensive areas of the contralateral cortex, so that cortical spread would cover less distance and involve smaller delays in the later activated hemisphere. Secondly, cortical spread through areas of the sensorimotor cortex in the later activated hemisphere representing body parts distal and contralateral to the initial focus of myoclonic activity will be facilitated by the simultaneous transcallosal excitation of these cortical areas following cortical spread from the initial focus in the first active hemisphere.

In many patients with cortical reflex or action myoclonus the myoclonic activity remains focal to the stimulated or active limb, with no evidence of intrahemispheric spread. This suggests that abnormal intrahemispheric spread of activity, like abnormal interhemispheric spread, represents an additional and separate pathophysiological abnormality in some patients with cortical myoclonus. This abnormal intrahemispheric spread of excitation via relatively rapidly conducting cortico-cortical pathways may also contribute to seizure generalization in myoclonic patients. This conclusion is supported by the observation that increased (^{14}C) deoxyglucose activity is most prominent in those cortical laminae receiving cortico-cortical connections during experimental seizure spread (Collins, 1978*b*).

Conclusion

Cortical reflex and action myoclonus, when present in their simplest forms, consist of an exaggeration of cortical long loop reflexes (Chauvel *et al.*, 1978; Hallett *et al.*, 1979; Deuschl *et al.*, 1987), and abnormalities in the intracortical processing of motor activity (Hallett *et al.*, 1979; Obeso *et al.*, 1985). In many patients additional deficits, again possibly an exaggeration of normal physiological mechanism, lead to more complex and extensive myoclonus. Abnormalities in the cortical inhibition following sensory stimulation (Sutton and Mayer, 1974; Ugawa *et al.*, 1991), and in the intrahemispheric and interhemispheric spread of excitation (the present paper) have been identified in cortical myoclonus. The abnormal intrahemispheric and interhemispheric spread of activity may be relevant to the generalization of seizures seen in these patients. In addition, the further study of these abnormalities may provide a model for seizure generalization in some forms of primary generalized epilepsy.

REFERENCES

Barker AT, Jalinous R, Freeston IL (1985) Non-invasive magnetic stimulation of human motor cortex. *Lancet*, **i**, 1106–1107.

Bird TD, Shaw CM (1978) Progressive myoclonus and epilepsy with dentatorubral degeneration: a clinicopathological study of the Ramsay Hunt syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry*, **41**, 140–149.

Brazier MAB (1972) Spread of seizure discharges in epilepsy: anatomical and electrophysiological considerations. *Experimental Neurology*, **36**, 263–272.

Brodal A (1981) *Neurological Anatomy: In Relation to Clinical Medicine*. Third edition. New York: Oxford University Press.

Chauvel P, Louvel J, Lamarche M (1978) Transcortical reflexes and focal motor epilepsy. *Electroencephalography and Clinical Neurophysiology*, **45**, 309–318.

Collins RC (1978*a*) Kindling of neuroanatomic pathways during recurrent focal penicillin seizures. *Brain Research, Amsterdam*, **150**, 503–517.

Collins RC (1978*b*) Use of cortical circuits during focal penicillin seizures: an autoradiographic study with [^{14}C]deoxyglucose. *Brain Research, Amsterdam*, **150**, 487–501.

Cracco RQ, Amassian VE, Maccabee PJ, Cracco JB (1989) Comparison of human transcallosal responses evoked by magnetic coil and electrical stimulation. *Electroencephalography and Clinical Neurophysiology*, **74**, 417–424.

Day BL, Rothwell JC, Thompson PD, Dick JPR, Cowan JMA, Berardelli A *et al.* (1987) Motor cortex stimulation in intact man: 2. Multiple descending volleys. *Brain*, **110**, 1191–1209.

DeFelipe J, Conley M, Jones EG (1986) Long-range focal collateralization of axons arising from corticocortical cells in monkey sensory-motor cortex. *Journal of Neuroscience*, **6**, 3749–3766.

Deuschl G, Schenck E, Lücking CH, Ebner A (1987) Cortical reflex myoclonus and its relation to normal long-latency reflexes. In: *Motor Disturbances I* Edited by R. Benecke, B. Conrad and C. D. Marsden. London: Academic Press, pp. 305–319.

Erickson TC (1940) Spread of the epileptic discharge: an experimental study of the after-discharge induced by electrical stimulation of the cerebral cortex. *Archives of Neurology and Psychiatry, Chicago*, **43**, 429–452.

Ferbert A, Priori A, Rothwell JC, Colebatch J, Day BL, Marsden CD (1990) Trans-callosal effects on motor cortical excitability in man. *Journal of Physiology, London*, **429**, 39*P*.

Gabbott PLA, Martin KAC, Whitteridge D (1987) Connections between pyramidal neurons in layer 5 of cat visual cortex (area 17). *Journal of Comparative Neurology*, **259**, 364–381.

Gasser HS (1950) Unmedullated fibers originating in dorsal root ganglia. *Journal of General Physiology*, **33**, 651–690.

Gotman J (1981) Interhemispheric relations during bilateral spike-and-wave activity. *Epilepsia*, **22**, 453–466.

Gotman J (1983) Measurement of small time differences between EEG channels: method and application to epileptic seizure propagation. *Electroencephalography and Clinical Neurophysiology*, **56**, 501–514.

Gould HJ, Cusick CG, Pons TP, Kaas JH (1986) The relationship of corpus callosum connections to electrical stimulation maps of motor, supplementary motor, and the frontal eye fields in owl monkeys. *Journal of Comparative Neurology*, **247**, 297–325.

Hallett M, Chadwick D, Marsden CD (1979) Cortical reflex myoclonus. *Neurology, New York*, **29**, 1107–1125.

Hauw JJ, Escourolle R, Baulac M, Morel-Maroger A, Goulon M, Castaigne P (1986) Postmortem studies on post-hypoxic and post-methyl bromide intoxication: case reports. *Advances in Neurology*, **43**, 201–214.

Hess CW, Mills KR, Murray NMF (1987) Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology, London*, **388**, 397–419.

HUNT JR (1921) Dyssynergia cerebellaris myoclonica—primary atrophy of the dentate system: a contribution to the pathology and symptomatology of the cerebellum. *Brain*, **44**, 490–538.

JENNER P, LEIGH PN, MARSDEN CD, REAVILL C (1981) Cortical involvement in forepaw myoclonus induced by intrastriatal administration of picrotoxin to rats. *British Journal of Pharmacology*, **72**, 503*P*–504*P*.

JENNY AB (1979) Commissural projections of the cortical hand motor area in monkeys. *Journal of Comparative Neurology*, **188**, 137–146

JONES EG (1985) *The Thalamus*. New York: Plenum Press.

JONES EG, POWELL TPS (1969) Connexions of the somatic sensory cortex of the rhesus monkey: II.—contralateral cortical connexions. *Brain*, **92**, 717–730.

JONES EG, COULTER JD, HENDRY SHC (1978) Intracortical connectivity of architectonic fields in the somatic sensory, motor and parietal cortex of monkeys. *Journal of Comparative Neurology*, **181**, 291–347.

KANG Y, ENDO K, ARAKI T (1988) Excitatory synaptic actions between pairs of neighboring pyramidal tract cells in the motor cortex. *Journal of Neurophysiology*, **59**, 636–647.

KAROL EA, PANDYA DN (1971) The distribution of the corpus callosum in the rhesus monkey. *Brain*, **94**, 471–486.

KISVÁRDAY ZF, MARTIN KAC, FREUND TF, MAGLÓCZKY Z, WHITTERIDGE D, SOMOGYI P (1986) Synaptic targets of HRP-filled layer III pyramidal cells in the cat striate cortex. *Experimental Brain Research*, **64**, 541–552.

KUGELBERG E, WIDÉN L (1954) Epilepsia partialis continua. *Electroencephalography and Clinical Neurophysiology*, **6**, 503–506.

KÜNZLE H (1975) Bilateral projections from precentral motor cortex to the putamen and other parts of the basal ganglia. An autoradiographic study in *Macaca fascicularis*. *Brain Research, Amsterdam*, **88**, 195–209.

LANCE JW, ADAMS RD (1963) The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain*, **86**, 111–136.

LHERMITTE F, TALAIRACH J, BUSER P, GAUTIER J-C, BANCAUD J, GRAS R *et al.* (1971) Myoclonies d'intention et d'action post-anoxiques: étude stéréotaxique et destruction du noyau ventral latéral du thalamus. *Revue Neurologique*, **124**, 5–20.

MARCUS EM, WATSON CW (1968) Symmetrical epileptogenic foci in monkey cerebral cortex. *Archives of Neurology, Chicago*, **19**, 99–116.

MILHORAT TH (1967) Experimental myoclonus of thalamic origin. *Archives of Neurology, Chicago*, **17**, 365–378.

MOTT FW, SCHAEFER EA (1980) On movements resulting from faradic excitation of the corpus callosum in monkeys. *Brain*, **13**, 174–177.

OBESO JA, ROTHWELL JC, MARSDEN CD (1985) The spectrum of cortical myoclonus. *Brain*, **108**, 193–224.

PAGNI CA, MAROSSERO F, CABRINI G, ETTORRE G, INFUSO L (1971) Physiopathology of stimulus sensitive myoclonus. a stereo-EEG study. *Electroencephalography and Clinical Neurophysiology*, **31**, 176.

PAINTAL AS (1978) Conduction properties of normal peripheral mammalian axons. In: *Physiology and Pathobiology of Axons*. Edited by S. G. Waxman. New York: Raven Press, pp. 131–144

PANDYA DN, VIGNOLO LA (1969) Interhemispheric projections of the parietal lobe in the rhesus monkey. *Brain Research, Amsterdam*, **15**, 49–65.

PATEL S, SLATER P (1987) Analysis of the brain regions involved in myoclonus produced by intracerebral picrotoxin. *Neuroscience*, **20**, 687–693.

PENFIELD W, BOLDREY E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, **60**, 389–443.

PURPURA DP, GIRADO M (1959) Synaptic mechanisms involved in transcallosal activation of corticospinal neurons. *Archives Italiennes de Biologie*, **97**, 111–139.

ROSENBLUETH A, CANNON WB (1942) Cortical responses to electric stimulation. *American Journal of Physiology*, **135**, 690–741.

ROTHWELL JC, THOMPSON PD, DAY BL, DICK JPR, KACHI T, COWAN JMA *et al.* (1987) Motor cortex stimulation in intact man: 1. General characteristics of EMG responses in different muscles. *Brain*, **110**, 1173–1190.

SHANKS MF, ROCKEL AJ, POWELL TPS (1975) The commissural fibre connections of the primary somatic sensory cortex. *Brain Research, Amsterdam*, **98**, 166–171.

SHIBASAKI H, YAMASHITA Y, KUROIWA Y (1978) Electroencephalographic studies of myoclonus: myoclonus-related cortical spikes and high amplitude somatosensory evoked potentials. *Brain*, **101**, 447–460.

SHIBASAKI H, YAMASHITA Y, NESHIGE R, TOBIMATSU S, FUKUI R (1985) Pathogenesis of giant somatosensory evoked potentials in progressive myoclonic epilepsy. *Brain*, **108**, 225–240.

SPIDALIERI G, GUANDALINI P, FRANCHI G (1986) Motor responses mediated by orthodromic and antidromic activation of the rostral portion of the cat corpus callosum. *Experimental Brain Research*, **64**, 133–142.

SUTTON GG, MAYER RF (1974) Focal reflex myoclonus *Journal of Neurology, Neurosurgery, and Psychiatry*, **37**, 207–217.

THOMPSON PD (1991) *Motor Cortex Stimulation in Man.* Ph.D. thesis, University of London.

THOMPSON PD, MAERTENS DE NOORDHOUT A, DAY BL, ROTHWELL JC, VAN DER KAMP W, MARSDEN CD (1989) Clinical and electrophysiological observations in post-anoxic myoclonus. In: *Neural Mechanisms in Disorders of Movement* Edited by A. R. Crossman and M. A. Sambrook. London. John Libbey, pp. 375–381.

UGAWA Y, GENBA K, SHIMPO T, MANNEN T (1991) Somatosensory evoked potential recovery (SEP-R) in myoclonic patients. *Electroencephalography and Clinical Neurophysiology*, **80**, 21–25.

VAN WAGENEN WP, HERREN RY (1940) Surgical divison of commissural pathways in the corpus callosum· relation to spread of an epileptic attack. *Archives of Neurology and Psychiatry, Chicago*, **44**, 740–759.

VOGT BA, PANDYA DN (1978) Cortico-cortical connections of somatic sensory cortex (areas 3, 1 and 2) in the rhesus monkey. *Journal of Comparative Neurology*, **177**, 179–191.

WADA JA, SATO M (1975) The generalized convulsive seizure state induced by daily electrical stimulation of the amygdala in split brain cats *Epilepsia*, **16**, 417–430.

WADA JA, NAKASHIMA T, KANEKO Y (1982) Forebrain bisection and feline amygdaloid kindling. *Epilepsia*, **23**, 521–530.

WADA JA, MIZOGUCHI T (1984) Limbic kindling in the forebrain-bisected photosensitive baboon, *Papio papio. Epilepsia*, **25**, 278–287.

WADA JA, KOMAI S (1985) Effect of anterior 2/3 callosal bisection upon amygdaloid kindling primarily generalized convulsions in the epileptic baboon, *Papio papio.* In: *Epilepsy and the Corpus Callosum.* Edited by A. G. Reeves. New York: Plenum Press, pp. 75–97.

WAXMAN SG, BENNETT MLV (1972) Relative conduction velocities of small myelinated and non-myelinated fibres in the central nervous system. *Nature: New Biology*, **238**, 217–219.

WILKINS DE, HALLETT M, BERARDELLI A, WALSHE T, ALVAREZ N (1984) Physiologic analysis of the myoclonus of Alzheimer's disease. *Neurology, Cleveland*, **34**, 898–903.

WILSON DH, REEVES AG, GAZZANIGA MS (1982) 'Central' commissurotomy for intractable generalized epilepsy: series two. *Neurology, New York*, **32**, 687–697.

WOOLSEY CN (1958) Organization of somatic sensory and motor areas of the cerebral cortex. In: *Biological and Biochemical Bases of Behavior*. Edited by H F. Harlow and C. N. Woolsey Madison: University of Wisconsin Press, pp. 63–81.

WOOLSEY CN (1964) Cortical localization as defined by evoked potential and electrical stimulation studies. In: *Cerebral Localization and Organization*. Edited by G. Schaltenbrand and C N. Woolsey. Madison: University of Wisconsin Press, pp. 17–26.

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BOOK REVIEWS

Neurology in Clinical Practice. Volumes I and II. Edited by W G. Bradley, R. B. Daroff, G. M. Fenichel and C D. Marsden. 1990. Pp 2160. London: Butterworth, Heinemann. Price £160 00.

Those neurologists remembered for their particular skills and accuracy of diagnosis had in common a profound knowledge of basic neuroanatomy and neurophysiology with an understanding of the processes of neuropathology. A life of busy clinical practice produced a bank of experience from which they would draw when faced with problems of diagnostic difficulty As a reflection of this requirement, most textbooks written in the immediate post-war years stressed the importance of basic anatomy and physiology and contained introductory chapters providing a simple background upon which the budding neurologist could base his forthcoming clinical experience.

With the evolution of neurological understanding and expertise these introductory chapters became somewhat superfluous and rather naive, written by the neurologist responsible for the single author text. There has also been a move away from single author textbooks for it is no longer possible to encompass the full range of neurological disease with great authority. The author now tends to aim his efforts at the undergraduate, emphasizing interest and style, brevity and 'essentials'. The available range has recently been improved by individual monographs devoted, for example, to movement disorders, infections of the nervous system, individual disease entities and investigations and treatment. These provide a more thorough coverage of the material and a more comprehensive consideration of the literature. Even in these small volumes multi-authorship has become popular, for the specialist has come to accept his limitations. Such monographs have proved very acceptable, with a competent editor putting together the views of his highly specialized colleagues. Unfortunately, and almost inevitably, their popularity and saleability have led to overproduction and a fall in the general standard. It is as though every worker accomplished in a particular field is obliged to write, or more readily edit, his monograph.

The serious student is again looking for a comprehensive text on neurological disease and these are being provided in increasing numbers. Some recently reviewed in this journal have been highly acclaimed. The trainee is now looking for a more composite book, not so much for the pure reading and learning of the subject but as a reference source, short of the original literature but adequate enough to offer a detailed description of a particular topic and allow it to be 'key referenced'. Paramount among the larger works has been the successful 'Handbook of Neurology' running to forty volumes and now well into its second edition. This exhaustive enterprise has unfortunately shown a great unevenness of writing and its selection of topics, and simply provides for most neurologists a source of entry into the old literature.

From the Americas we have received several multi-author multi-volume works notably Baker's *Neurology* and the beautifully produced *Clinical Neurosciences* under the senior editorship of Rosenburg. They have been joined by some recent contributions from the United Kingdom.

There are now many adequate well written and accurate multi-author large textbooks, each perhaps with a different emphasis on clinical appraisal, neuropathological significance and therapeutic possibilities. One would suggest, enough to satisfy the trainee market of the Western World, undaunted by the escalating cost of each However, in October 1990 Butterworths published the two volume work of four principal editors. With the help of eleven sub-editors, they have persuaded 131 contributing authors to offer their thoughts on topics of their special interest in *Neurology in Clinical Practice.* Volume I addresses the problems of diagnosis and management and volume II, the neurological disorders.

Just as Harrison's *Textbook of Medicine* dealt with the interpretation of specific symptoms in its first few chapters, so Part I of this book takes individual subjects, for example, drop attacks, visual disorders, etc., and deals with them on a differential diagnostic basis.

Part II is concerned with the investigation techniques currently available and Part III provides the usual didactic account of genetics, neuroepidemiology, virology and endocrinology, ophthalmology and otology. The fourth part discusses neurological management and the final section is devoted to a discussion of diseases of the nervous system, i.e. the standard textbook format adopted by most of the other current texts.

The senior editors of these volumes could be said to represent the younger schools of neurology and have enjoyed the opportunity to live through the explosion of knowledge in basic neuroscience, leaving the descriptive schools, and encompassing the expansion of the use of the laboratory in neurological investigation. They have benefited from the advent of computer science, perhaps the greatest advance in modern medicine which has led to the techniques of neuroimaging.

The editors have provided us with a practical textbook of neurology, laid out in a new format and encompassing the recent technology of investigation and treatment, comprehensively and instructively set out. They aim their work at neurologists in training and those established in practice as well as generalists and their related disciplines. They offer a general outline of disease of the nervous system, an assessment of pathophysiology and a refreshingly practical new approach to diagnosis and management. They assume in their readership a knowledge of basic neurological science and expect the reader to have a sound understanding of the basic structure and function of the human nervous system and of general medicine. This is an innovative change and a great advantage over the work of the previous authors and some of their competitors.

The editors have restricted their references in individual chapters to sources of real importance and have resisted the trend towards what are often incomplete bibliographies. This approach should be welcomed. The extent to which they have succeeded will be reflected in the popularity or otherwise of this first edition. This reviewer found the volumes attractive. There is some evidence of uneven editing and some topics are quickly and superficially dismissed whereas others are given perhaps more prominence than they deserve. This is always a problem in multi-author texts and may simply reflect the interest and enthusiasm of the writer. The larger sections in this volume are better written and more informative. Psychiatry is kept to a minimum which is appropriate in a textbook on neurology, but separate sections are devoted to the neurology of the elderly, the neurology of pregnancy and there is a very important chapter on the neurological problems of the newborn where there have been so many advances in recent years.

Time does not allow any reviewer carefully to read over 2000 pages of double columned text but simply to select certain chapters and enjoy them individually.

These two volumes combine the best of British and American neurology. The provenance of the senior editors is well known. They are all gifted writers and have enlisted a very distinguished team of authors from the younger schools of neurology in the United Kingdom and America. The overall impression is that this will be a successful book. It is certainly a major contribution to the neurological literature and will sit comfortably on the shelves with its peers. The publication will appeal to libraries rather than individual purchasers but will suffer the fate of its older competitors in requiring early revision. The revision of 131 separate contributions will be a mammoth task, almost as daunting as the original concept and task of producing this first edition.

JOHN B. FOSTER

Focal Epilepsy: Clinical Use of Emission Tomography. Edited by M. Baldy-Moulinier, N. A. Lassen, J. Engel and S. Askienazy. 1990. Pp. 216. London: John Libbey. Price £28.00.

This volume consists of the proceedings of a symposium held in May 1989 on the clinical use of functional imaging in focal epilepsy. As such, the 20 chapters are largely repetitive and there is little evidence of active editing. Engel provides a useful review of terminology, the neurobiological basis of epileptogenesis, and the role of Positron Emission Tomography (PET) in presurgical evaluation. Lassen's account of Single Photon Emission Computed Tomography (SPECT) blood flow tracers is clear and readable. There are two chapters on SPECT methodology that have a significant overlap, and the account of PET methodology is superficial. There are 13 contributions relating to the clinical use of cerebral blood flow imaging in patients with partial seizures, that vary in their depth, quality and degree of critical appraisal of their results. The best two chapters in this section of the book are those by Habert *et al.* and by Rowe *et al.* There are some interesting side issues presented within the main thrust, such as the report of increased blood flow in cortical motor areas at the time of a definite pseudoseizure, and a preliminary report on the effects of hyperventilation on tracer uptake in patients with partial seizures. At the end of the volume there is a very clear, concise summary and overview of the field by Lassen.

This book will be of interest to those who are planning to use SPECT with interictal and ictal blood flow imaging in the presurgical evaluation of patients with partial seizures.

JOHN S DUNCAN

Neuromuscular Transmission: Basic and Applied Aspects. Edited by Angela Vincent and Dennis Wray. No. 12 in the series *Studies in Neuroscience.* 1990. Pp 294. Manchester: Manchester University Press. Price £50.00.

This volume covers practically all aspects of the neuromuscular junction from physiology to molecular biology and to clinical implications. The neuromuscular junction, in particular its neurotransmitter receptor, the acetylcholine receptor (AChR), has been a prototype example in neurobiology research. The AChR was the first neuroreceptor of which function, biochemistry and structure was defined. Furthermore, the human disorder myasthenia gravis which is characterized by neuromuscular transmission failure was identified as an autoimmune disorder of the AChR. Finally, a number of other naturally occurring human disorders have been nailed down by identifying the characteristic neuromuscular transmission abnormality or even defining the defective molecule. These include the Lambert-Eaton myasthenic syndrome and an ever increasing number of rare congenital transmission disorders. There have been several smaller and larger review articles and books emanating from international conferences (Drachman, 1987, de Baets *et al.*, 1988). In contrast to these volumes covering a large number of research papers and only a lmited number of reviews, the present book is the first up-to-date summary of what is known about the neuromuscular junction. The readership to which it is addressed includes basic science and postgraduate students as well as clinical research workers.

The volume is divided in 13, mostly single-authored chapters bringing together leading experts and active scientists who have experience in this field for 10 years and longer. In the introductory chapter by C. Slater and A. Vincent the principles of neuromuscular structure and development are outlined, including more recent molecular work on neuromuscular junction proteins such as neural cell adhesion molecule (N-CAM) and agrin. It also summarizes the effects of experimental manipulations of the neuromuscular junction. A second introductory chapter by D. Wray covers principles of neuromuscular transmission and a third one is a brief account on research methods that are used in studies of the neuromuscular junction. All introduction chapters are well referenced including cross-references to forthcoming chapters.

The following chapters by P. Molenaar on the neurotransmitter acetylcholine and its pharmacology, by R. Norman and by D. Dolly on structure and function of neuromuscular ion channels and on the role of pre- and postsynaptic neurotoxins and channel blockers are very helpful reviews based on a large body of the author's own experience. The following chapter by D. Colquhoun is a concise and didactic review of the action of agonists and antagonists in terms of electrophysiologic analysis. The following two chapters by D. Beeson and E. Barnard, and J. Lindstrom respectively, deal with the biochemistry and molecular biology of the acetylcholine receptor. The inter-species differences between mammalian and non-mammalian receptor synthesis, AChR metabolism, its structural transmembrane arrangement, and the role of various peptides as immunologic epitopes are all covered, much of which comes from the authors' laboratories.

The remaining four chapters deal with human and animal disorders occurring both naturally and experimentally. The chapter on congenital myasthenic syndromes by A. G. Engel lists well-characterized and three partially characterized syndromes of genetically linked neuromuscular transmission disorders most of which have been first described or even precisely defined by the authors' group. Some of these syndromes extend beyond the neuromuscular junction and the molecular defects are not understood. These 'experiments of nature' are a challenge to basic scientists interested in neuromuscular transmission. The following chapter by A. Vincent on acquired autoimmune myasthenia gravis, the prototype neuromuscular disorder, briefly reviews the basic features and the essence of a huge scientific opus to which the author has contributed profoundly. It deals in some detail with immunologic heterogeneity at the antibody (B-cell) and the T-cell level which limits antigen-specific immunotherapy. Chapter 12 by D. Wray reviews the exciting discoveries on the second autoimmune neuromuscular transmission disorder, the Lambert-Eaton myasthenic syndrome. The chapter clearly outlines the molecular defect and the putative link to small cell carcinoma of the lung.

The final chapter by M. de Baets deals with experimental autoimmune myasthenia gravis (EAMG) in laboratory animals. The studies on EAMG revealed many insights in the molecular pathology of myasthenia gravis and into the biochemistry of the AChR. The role of antibody diversity and the hypothetic role of idiotype-network dysregulation is presented with reference to human myasthenia gravis.

The editors and authors of this book have reached their goal in presenting a multidisciplinary approach to the neuromuscular transmission at a high scientific level. The book is nicely presented with many tables and figures from both published and unpublished work. One can read the chapters out of the context of the entire book. Cross-referencing is widely used and appreciated. Only the photographic presentation of micrographs is poor. Here the reader should go to the original papers or textbooks from which these pictures were taken. The number of references was purposely restricted but many of the classic papers from the sixties and seventies, which opened the field to modern research, are included. Although much of the information contained in this book can be gathered elsewhere in the literature the book can be recommended without hesitation.

References

DRACHMAN DB, DE SILVA S, RAMSAY D, PESTRONK A (1987) Humoral pathogenesis of myasthenia gravis. *Annals of the New York Academy of Sciences*, **505**, 90–105.

Myasthenia Gravis. 1988. Edited by M. H. de Baets, H. J G. H. Osterhuis and K. V Toyka. Basel: Karger.

KLAUS TOYKA

Handedness and Developmental Disorder. By D. V. M. Bishop. 1990. Pp. 219. Oxford: Blackwell Scientific Publications. Price £21.00.

Laterality research has been described as a bog, and handedness must be its deepest mire There are deposits of superstition, folklore, clinical impression, poor research, and questionable statistics. The ground is frequently churned up by new theories paying no attention to tracks laid by previous workers. Dorothy Bishop brings some special qualities to this review: formidable powers of critical analysis, a scholar's respect for detail, an advocate's search for weakness in the argument and she is herself a left-hander. The combination guarantees a fresh, determined attack on the task of excavation. Each chapter gives a pithy review of the literature, an analysis of the main issues, and a concise concluding summary. The worst of the humbug is often dismissed in a sentence or two, giving a lightness of style and an economy of words which makes this short book full of matter. Not only is it an essential text for all who work in the fields of laterality and of developmental disorder but it is also a good read.

Left handedness could be boringly trivial, or it could be of great importance as an index of patterns of cerebral functional organization. In the developmental disorders, handedness could have implications for diagnosis and prognosis, or again it could be irrelevant. The case for the widely held belief that it is non-trivial and relevant is far from certain. The first six chapters review handedness as a natural phenomenon. There are nine chapters considering the effects of early brain damage and what is known about handedness in developmental disorders including epilepsy, mental handicap, autism and Rett syndrome, specific reading retardation, specific developmental disorders of speech and language, and stuttering. An appendix gives instructions and norms for some commonly used assessments of preference and skill.

The first question tackled concerns the nature of the skills and types of motor control likely to be associated with handedness, in the sense of consistent preference for one side. Through an original analysis of previous data, actions are identified where consistency is typical in comparison with others where it is not. Manipulations requiring the precision grip as in the control of a pen, practised aiming as in throwing, or two-handed skills such as batting at cricket or playing a guitar are associated with high levels of consistent preference, while actions such as carrying a suitcase or opening the lid of a box are not. The question of consistency at the level of the particular action is important because questionnaires which include actions of the latter type seriously inflate estimates of the incidence of left handedness. Consistency is also important in considering development because a child may be inconsistent when first learning how to perform a skilled action. This can lead to overestimates of mixed and left handedness, which are then mistakenly believed to decline with age. Questions about inconsistency at the level of action are considered at several points in the book. It is suggested that inconsistent or 'random' handedness for specific actions might be particularly relevant to the developmental disorders and worth further research.

Two other levels of inconsistency are distinguished, those of the individual and of the species. Some people always write with the left hand and always throw with the right. There is a very large number of such patterns of mixed hand preference in a substantial proportion of the normal population. In thinking about the development of handedness in the individual, it is important to distinguish random from mixed handedness At the species level, it is obvious that humans tend to prefer the right hand more often than the left, but are species asymmetries present in non-human primates? In theories about evolutionary origins, the degree of human consistency is often exaggerated in the search for precursors of human asymmetries in other species. Several explanations of the human bias to dextrality are considered including cultural influences, birth position and early handling but the most important, cerebral asymmetry for speech, is given its own chapter

This account of physical and functional asymmetries of the brain and their relation to handedness stays close to the typical presentation in the literature. There is an unfortunate tendency in that literature to combine data from several studies which have different proportions of left-handers, presumably because different criteria of sinistrality were used. It is particularly unfortunate when there are different incidences between dysphasic and non-dysphasic patients in the same series because this suggests that the criteria of left handedness were lenient for dysphasics, especially those with right sided lesions. Inferences about the cerebral control of speech in right and left handers cannot be based on such evidence. The critical stance here was not as tough as it could have been.

Theories of a genetic influence on handedness are described with rare clarity. I must acknowledge the space given to my own right shift theory here and elsewhere in the book. The treatment is generally sympathetic, if not always as firmly in support as I could wish. The normal development of handedness is given close attention, as expected in a book about developmental disorders. The chapter on the definition and measurement of handedness exposes the methodological inadequacies of the typical approach using handedness questionnaires. The difficulties of the alternative, measures of proficiency in tasks of hand skill, are also acknowledged. One of the arguments against proficiency measures has been the very different shapes of the distributions of asymmetries for skill and for preferences. The former have been known to be 'bell-shaped' since data collected by Galton, while the latter are typically 'J' shaped. The author has shown that the latter is mathematically predictable from the former. There is a brief but cogent chapter on the implications of handedness for cognitive abilities. It is not surprising that theories of intellectual deficit in left handers are found unconvincing but it is a pleasure to see the so-called 'evidence' demolished.

The developmental disorders are introduced through a chapter on early brain damage. The author's own research in this field was inspired by a type of 'statistical thought experiment' initiated by Paul Satz in the early seventies, which asked, 'what would be expected when left handedness is influenced by pathological factors that change the probabilities of manifestation?' Human reasoning is notoriously weak in estimating base rate probabilities and in assessing the significance of changes in frequency. It is salutory to see the smallness of expected changes for handedness following early unilateral brain damage. The interpretation of evidence, however, still depends on assumptions about the causes of handedness and about how abnormal changes might affect the phenotype. It is clear that some left handedness is due to early pathology, since some children have right hemiplegia. The question is whether raised incidences of left handedness are typical in any other developmental disorder. The answer is certainly 'yes' for the mentally hanicapped and for conditions where early brain damage is likely, but it is not obviously true for any other disorder when the mentally handicapped are excluded.

The chapters on speech disorders and dyslexia give overviews of a large literature and are particularly well informed through the author's own considerable research on language development. However, the differing meanings of 'left handedness' for the several studies reviewed, when some classify for 'mixed-handedness' while others do not, makes interpretation difficult. After a century of speculation about the existence of anomalies of cerebral dominance in cases of developmental language disorder, the evidence is weak and conflicting.

The final main task is to examine the suggestion of the late Norman Geschwind that several phenomena might depend on developmental anomalies of cerebral dominance. Left handedness, dyslexia, dysfunctions of the immune system, and gender differences in normal levels of visuospatial ability and in the frequency of developmental language disorders were all supposed to be linked through mechanisms involving the balance of sex hormones, and a retarding influence of testosterone on left hemisphere growth. Geschwind would almost certainly have defended his theory by saying it was intended to be a preliminary and forward looking integration of a large body of research findings. His ideas have commanded considerable attention and are a major influence on current approaches to laterality. This book does an important service by systematically examining key facets of the theory, giving credit where possible but showing the inconsistencies, disregard for contrary evidence and overinclusive speculation. The scholarly approach is particularly admirable here, when one is tempted to dismiss the theory as the latest accretion to the midden.

What should be done with a midden? After an excavation using the finest archaeological tools, the final survey reveals the extent of some appalling methodological and theoretical muddles. It is acknowledged that previous recommendations to abandon the field entirely could have been sound. The author cannot quite accept that there is no hidden treasure worth a further dig, but the reader has been given every chance to make a personal decision.

For my part I have long believed that Hercules' solution was required, a fresh stream to wash away the mess My efforts in this direction seem here merely to run into the bog. Is it possible to pinpoint the problem? For all its critical acumen, the book still accepts that handedness is a phenomenon which might have significance for something more important than itself. The right shift theory suggests that handedness is due to chance, and thus any theory which treats handedness as having specific foundations is bound to collapse. The features which attract people to the field are due to individual differences in cerebral specialization, but left handedness is virtually useless as an indicator of the differences that matter. The author's recommendation to study 'random' handedness could be a prescription to pursue a fleeting stage in the growth of characteristics which are themselves due to chance accidents of development

The legend says that Hercules diverted two streams. Clearly, more work is required to lay bare the true bases of these phenomena.

Marian Annett

Cognitive Neuropsychology. By R. A. McCarthy and E. K. Warrington. 1990. Pp. 438. San Diego: Academic Press. Price $34.95.

In the last 20 years a new approach in the investigation of the behavioural disorders produced by brain lesions has come to the fore: cognitive neuropsychology. The main feature distinguishing cognitive neuropsychology from the behaviourist views which dominated the field in the preceding years is the application of information processing models of human cognition to the analysis of deficits such as aphasia, amnesia, neglect. The present influence of cognitive neuropsychology is witnessed by the publication of a journal (*Cognitive Neuropsychology*) and of textbooks specifically devoted to this approach. The use of information processing models has led cognitive neuropsychologists to abandon the traditional syndromes, such as the Wernicke-Lictheim taxonomy of the aphasias. Neuropsychological disorders have been re-visited and re-interpreted in the light of box-and-arrow functional models. While this is the core of cognitive neuropsychology, shared by most scientists working in the field, there are areas of debate and conflict on a number of relevant methodological issues. For instance, should research be confined to the study of individual patients, or may group studies too provide useful information as to the functional architecture of the mind and its disorders? Is the concept of symptom-complex or syndrome of any use? Has double dissociation between symptoms any special role in neuropsychological investigation? Are anatomo-physiological data of any relevance?

In their textbook, McCarthy and Warrington give their answers to these extensively debated issues by an empirical approach. Rather than using a logical-deductive method, whereby information processing models of some human faculties are applied to neuropsychological disorders observed in patients, with the aim of interpreting them, McCarthy and Warrington first summarize the empirically observed patterns of impairment, and, second, make attempts at interpretations in the light of cognitive models. In this part competing interpretations are discussed and reference is made to the more theoretically motivated studies.

Each chapter of the book has a basic structure including five main sections. An introduction gives a brief historical background and some fundamental operational definitions. In the second section of each chapter ('empirical characteristics') disorders of human skills such as object recognition, spatial perception or sentence comprehension are described, mainly with reference to the observed dissociations between symptoms. The observed patterns of impairment are, to a lesser extent, considered in terms of the behavioural tasks used. For instance, in the chapter on spatial perception, patterns of defective performance in tests of line bisection, cancellation, orientation are described. In line with the information processing approach discussed above, little reference is made to the classical syndromes, which are often mentioned parenthetically. For instance, one does not find Balint's syndrome in the subject index. A notable exception is the chapter on object recognition, in which Lissauer's distinction between apperceptive and associative disorders is basically maintained in the modern information processing taxonomy. The review of the empirical literature, however, is not confined to the more recent cognitive studies, but relies heavily on both the classical studies and on research carried out after World War II in groups of patients. The overall emerging picture shows a strong continuity in the evolution of neuropsychological research. The basic common feature of the 19th century anatomo-clinical approach and of contemporary cognitive neuropsychology, as noted by McCarthy and Warrington in their introduction (chapter 1), is that the classical and modern diagrams share the basic concept of modular architecture, even though important differences exist, such as the relations with anatomy. The empirical sections of each chapter also make clear to the reader that McCarthy and Warrington consider both group and single case studies potentially useful sources of information for cognitive neuropsychologists, even though in recent years cognitive research has more frequently involved individual patients. The issue, which has given rise to extensive and somewhat lengthy debates in specialized journals, is not explicitly discussed, but the reviewed data clearly illustrate the contributions of either type of study.

The third section, termed 'anatomical considerations', discusses the neurological correlates of the empirically observed patterns of neuropsychological impairment. The neurological information is derived from the analysis of the localization of the lesion in patients with specific neuropsychological deficits, as assessed by post-mortem examination, CT-scan, MRI, neurosurgery, and, much less frequently (*see* p. 140), by Positron Emission Tomography (PET). All these methods except PET (*see below*) provide structural information concerning the site and size of the lesions. The result is a correlation between specific lesions of the left and/or right hemisphere and the observed patterns of neuropsychological impairment. This may take the form of a correlation between classical neuropsychological disorders (e.g. apperceptive and associative agnosia) and specific lesion sites. The correlation is sometimes made with impaired performance in specific tasks (e.g. single point localization, production of familiar and unfamiliar gestures, phoneme-matching disorders). The anatomical correlation is also made with the functional components of the cognitive system discussed in the theoretical section of each chapter. This is the case of the disorders of different subcomponents of short-term memory (auditory-verbal, visuo-verbal, visuo-spatial) and, with somewhat less clear cut results, of the reading and spelling systems (e.g. reading and spelling by sound and by vocabulary). These different levels of anatomical correlation illustrate the difficulty of the enterprise of investigating the neural basis of cognitive function. The overall pattern emerging from McCarthy and Warrington's treatment of the issue is that of a correlation between specific patterns of impairment and specific lesion sites. On the basis of data of this sort the inference can be made (bearing in mind Hughlings Jackson's caveat on the difference between localizing a lesion and localizing a function) that the neural correlates of specific cognitive systems are discrete cerebral regions It is noteworthy in this respect that McCarthy and Warrington do not mention the recent evidence from functional methods capable of measuring regional cerebral blood flow and metabolism. In normal individuals these techniques, which have been used to investigate the neural correlates of cognitive activities such as single word processing and visual attention, have confirmed and further specified the modular architecture of the neural systems involved in cognition, originally suggested by the traditional anatomo-clinical correlation studies. In brain-damaged animals and humans the imaging methods have shown a functional derangement in cerebral areas far removed from the structural lesion (a revisited version of von Monakow's concept of diaschisis). These recent findings also suggest that the neural correlates of mental functions may be better conceived in terms of the activity of specific complex neural circuits, including both connected cortical regions and some subcortical structures

In the fourth section of each chapter ('theoretical considerations') the empirical database is interpreted in the light of box-and-arrow functional models. The level of articulation of these models shows a considerable degree of variability in the different areas of cognition, ranging from the dichotomies used in the amnesia literature (procedural/declarative, semantic/episodic memory) to the more detailed flow charts describing linguistic processes such as reading. McCarthy and Warrington, as appropriate for a clinical introduction, often make use of descriptive, basic or generic frameworks of the different processes involved, the reader being referred to more specific references for further details. The great heuristic role of the double dissociation in shedding light on the multi-componential architecture of the cognitive system is clearly illustrated by numerous examples throughout the book (e.g. category-specific deficits in auditory comprehension and retrieval of individual words) This is contrasted by McCarthy and Warrington with the ambiguities of the associations of symptoms, which may reflect either the anatomical contiguity of the neural structures involved or the impairment of a single functional component, or both factors. McCarthy and Warrington take, however, a perhaps too pessimistic view when they write that 'it is virtually impossible to establish that impairments on two tasks are attributable to a single functional deficit' (p. 19). To give an illustrative example, the defective performance of some patients in a range of tests including digit span, the Brown-Peterson task, recency in free recall has been interpreted by a number of investigators, including the authors themselves, in terms of the selective impairment of a single component of verbal memory (auditory-verbal short-term memory).

Finally, each chapter terminates with a conclusion, which summarizes the content of the behavioural, anatomical and theoretical sections.

Making use of this basic framework (empirical characteristics, anatomical and theoretical considerations), McCarthy and Warrington review in 15 chapters the neuropsychological impairments of recognition and spatial perception, voluntary action, speech (word and sentences) comprehension and production, reading, writing and spelling, calculation, short- and long-term memory, planning and problem solving. The reader is provided with information adequate for a basic understanding of the main behavioural and neurological features of each pattern of impairment, together with essential historical data. Ample reference is made to the original papers, allowing the interested reader a more in-depth knowledge of the different topics. Since the book is meant as a 'clinical introduction' to cognitive neuropsychology, I miss, however, a chapter (or a section within each chapter) summarizing McCarthy and Warrington's suggestions and guidelines for an adequate and comprehensive assessment of cognitive functions in neurological patients. Such indications may of course be inferred from the empirical section of each chapter, but I wonder how easy an enterprise this might be for the non-expert reader. Such a section devoted to neuropsychological assessment would have benefited from the wide experience of the authors, who are not only distinguished scientists, but also practising neuropsychologists.

In summary, the book is an excellent introduction to contemporary neuropsychology, which illustrates the fruitful interaction between the clinical neurological tradition and the information processing approach of cognitive psychology. In their introductory chapter (pp. 20–1) McCarthy and Warrington cautiously wonder whether the next 20 years will bring back antilocalizationist views such as mass-action and globalism. While McCarthy and Warrington's wary attitude is to be appreciated, the resurgence of holistic perspectives appears most unlikely, in the light of both the anatomical evidence reviewed in the book and the physiological studies investigating the metabolic and blood flow correlates of specific cognitive activities. The book will have much appeal to all students of the behavioural disorders produced by brain lesions, both neurologists and cognitive psychologists.

GIUSEPPE VALLAR

Peripheral Nerve Lesions. Diagnosis and Therapy. Edited by M. Mumenthaler and H. Schliack. 1991. Pp. 416. Stuttgart: Georg Thieme. Price DM 198.00.

When one drives from Italy into Switzerland, a Swiss friend once told me, one immediately knows when the border has been reached because stones marking the verge of the road abruptly become arranged in neat lines. Such attention to detail is part of the Swiss character and is clearly discernible in this book; no stone is left unturned. The book in which five of the seven principal contributors are Swiss, represents their accumulated experience on the clinical, diagnostic and surgical aspects of peripheral nerve lesions.

The book first appeared in German in 1966 and has been through five editions, the last published in 1987. This is the first edition to be translated into English.

The book is logically organized with introductory sections on the embryology, anatomy and physiology of peripheral nerves, followed by a detailed account of the clinical examination of patients. Subsequent sections are organized topographically with individual peripheral nerve or plexus lesions covered from the aetiological, clinical, differential diagnostic and therapeutic viewpoints. The illustrations, a mixture of line drawings, clinical photographs and anatomical diagrams have been produced with high resolution. Another notable feature of the book is the summarizing tables giving pointers to the differential diagnosis in defined situations. The referencing is comprehensive; over 2000 references have been placed at the end of the book, numbered and arranged alphabetically. Not surprisingly, a fair proportion of the references are from the German literature. The index works.

A reviewer naturally dips into a book of this type and sees how his experience of certain clinical entities tallies with those of the authors. I chose first the carpal tunnel syndrome. The clinical description is complete emphasizing as almost pathognomonic the feature of 'brachialgia paresthetica nocturna' and mentions a long list of pathogenetic factors, of which the description of carpal tunnel syndrome secondary to A-V fistulae for haemodialysis is particularly useful. My pen twitched only once in the neurophysiology section when an old reference was quoted showing that 85% of patients had prolonged distal motor latencies; with earlier referral, this is now certainly an overestimate. I was pleased with the discussion of the relative merits of hydrocortisone injection; the authors contend that this should only be undertaken once and then '. . . not in cases of demonstrable neurological deficit or of abnormal neurophysiological findings . . .'. Peculiarities in the course of median nerve branches at the wrist, particularly the recurrent motor branch, are quoted as, in themselves, contraindications against the use of a small incision or the retinaculotome.

I turned my attention next to neuralgic amyotrophy which the authors term 'neuralgic shoulder amyotrophy' eschewing the older terms 'plexus neuritis' and 'brachial neuritis' as being less descriptive. Again the description corresponded with my own experience apart from the contention that the disease is benign even though the authors quote a series of 44 patients of which 32 still had objective deficits after 7 years; in my view, neuralgic amyotrophy is often not so benign.

Next I turned to the thoracic outlet syndrome, the diagnosis and treatment of which is controversial, differing greatly on the two sides of the Atlantic. The authors are quite clear where they stand and conform to the English view. They begin the section 'A thoracic outlet syndrome in our opinion is diagnosed too frequently and without sufficient objective evidence. We have seen numerous patients who underwent unnecessary surgery, and the presence of diffuse brachialgia is no reason to assume a thoracic outlet syndrome.' Again my pen twitched in the neurophysiology section where the authors assert that '. . . the F-wave in latency is clearly delayed . . .' (this should read 'prolonged' in the next edition) but is in any case counter to my experience and others quoted in the references.

There is a sprinkling of irritations throughout the book stemming mainly from its translation from the German. Action potentials are occasionally 'registered' rather than 'recorded'. Diagnostic localization is referred to as 'localizational diagnosis' In the symptomatology of carpal tunnel syndrome '. . . the first routines of the day, such as *washing up* and getting dressed, are difficult . . .'; this may of course be a reference to the Swiss routine. The reference to Dawson and Scott as the originators of the averager for sensory action potential recording has been misspelled. And curiously the term 'entrapment neuropathy' is never used at all. Despite these minor carpings, the translator is to be congratulated on what must have been a monumental and difficult exercise.

The book then can be recommended by virtue of its balanced viewpoints, its comprehensive coverage, its excellent clinical descriptions and the clarity of its illustrations and tables. Neurologists, Clinical Neurophysiologists and Neurosurgeons interested in the peripheral nerves will find this a valuable reference work.

K. R. MILLS

ANNOUNCEMENTS

Community Care for Elderly People with Dementia – Psychosocial Issues

A one-day symposium will be held at the Institute of Psychiatry, London, on November 18, 1991. For further information please contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel 071 703 5411 ext. 3170).

BMDP PC for Multivariate Analysis

This course will be held at the Institute of Psychiatry, London, on December 10–12, 1991. It will give an introduction to BMDP PC and its use in the analysis of multivariate data For further information please contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel: 071 703 5411 ext. 3170).

Recent Advances in Couple Therapy

This 3-day conference will be held at the Institute of Psychiatry, London, on January 29–31, 1992. For further information please contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel 071 703 5411 ext 3170).

International Symposium on Neuroimaging in Psychiatry

The symposium will be held at the Institute of Psychiatry, London, on February 3–4, 1992. For further information please contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel. 071 703 5411 ext. 3170)

IX International Congress of Electromyography and Clinical Neurophysiology

The congress will be held in Jerusalem, Israel, on June 8–12, 1992. It will present the state of the art in EMG and will focus on clinical topics as well as basic research in neurophysiology For information contact Dr. Arieh N Gilai, Convener, EMG–CN–IX Congress, PO Box 29334, Tel Aviv 61292, Israel (Tel 972 3 5102542; Fax: 972 3 660604, Telex: 33554 INTUR IL)

European Neurological Society

The third meeting will be held at the Palais de Beaulieu, Lausanne, Switzerland on June 27–July 1, 1992 The deadline for the receipt of abstracts is January 15, 1992 Further information may be obtained from Professor Andreas Steck, Service de Neurologie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.

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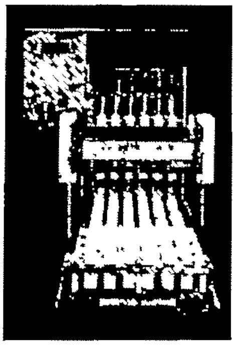

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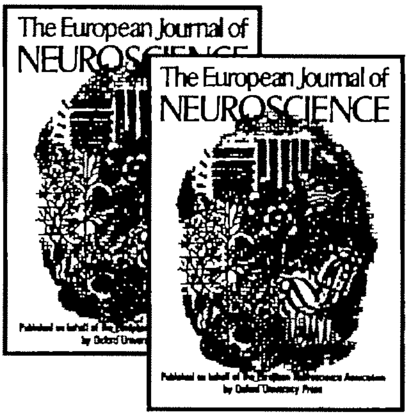
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1. Mumford JP.Br J Clin Pract 1988; 42 (Suppl 61): 7-9

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METABOLIC PATTERNS ASSOCIATED WITH NON-SPECIFIC MAGNETIC RESONANCE IMAGING ABNORMALITIES IN TEMPORAL LOBE EPILEPSY

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SUMMARY

We investigated the cerebral metabolic patterns associated with non-specific hyperintense T_2-weighted image on Magnetic Resonance Imaging (MRI) in Temporal Lobe Epilepsy (TLE). Nineteen patients suffering from TLE with a normal CT scan underwent Positron Emission Tomography (PET) using ^{18}F-fluorodeoxyglucose; 8 had hyperintense T_2-weighted image on MRI in the epileptogenic temporal lobe and 11 had a normal MRI. Interictally, PET exhibited focal hypometabolism in all the patients with hyperintense T_2-weighted image and in 8 of the 11 whose MRI was normal. The hypometabolic area was significantly more extensive in patients with hyperintense T_2-weighted image in whom it always encompasses the site of the MRI abnormality. Moreover, these patients had higher metabolic asymmetry index in the temporal and parietal lobes than patients with a normal MRI. One patient with mesial temporal hyperintense T_2-weighted image underwent an ictal PET, which showed that the focal hypermetabolism fitted remarkably with the site and size of the abnormal MR signal. Thus, non-specific hyperintense T_2-weighted images are associated with particular interictal and ictal metabolic patterns which might suggest that these MRI abnormalities reflect an epileptogenic lesion.

INTRODUCTION

In Temporal Lobe Epilepsy (TLE), Magnetic Resonance Imaging (MRI) discloses several types of signal abnormalities undetected on CT scan (Abou-Khalil *et al.*, 1984; McLachlan *et al.*, 1984; Riela *et al.*, 1984; Sussman *et al.*, 1984). Non-specific hyperintense T_2-weighted image concordant with the location of the scalp-EEG focus is the most frequent of these MRI abnormalities (*see* Table 1 for a review). However, the relationships of this type of abnormal MR signal to the epileptogenic activity and the related pathological findings are still unclear. Ictal discharges on stereotaxic EEG recordings, though largely concordant, do not match exactly the site of the MRI abnormality in all cases (Rougier *et al.*, 1988). Gliosis was found to be the most frequent pathology associated with hyperintense T_2-weighted image (McLachlan *et al.*, 1985; Lesser *et al.*, 1986; Grant *et al.*, 1987; Kuzniecky *et al.*, 1987; Jackson *et al.*, 1990), but tumours and normal tissue have also been observed (Bergen *et al.*, 1985; Jabbari *et al.*, 1986; Sperling *et al.*, 1986; Kuzniecky *et al.*, 1987; Schorner *et al.*, 1987; Rougier *et al.*, 1988; Heinz *et al.*, 1990; Jackson *et al.*, 1990). On the other hand, MRI was reported as normal in several

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TABLE 1. MRI ABNORMALITIES IN PATIENTS WITH TEMPORAL LOBE EPILEPSY AND NORMAL CT SCAN

Authors	*Cases studied*	*Abnormal MRI*		*Non-specific hyperintense T_2-weighted images concordant with EEG data*	
	No	*No.*	*%*	*No*	*%*
McLachlan *et al.* (1985)	16	14	(87)	7	(44)
Jabbari *et al.* (1986)	22	5	(23)	2	(9)
Lesser *et al.* (1986)	10	3	(30)	3	(30)
Radtke *et al.* (1986)	14	4	(29)	3	(21)
Sperling *et al.* (1986)	27	5	(18)	1	(4)
Theodore *et al.* (1986)	19	4	(21)	3	(16)
Abou-Khalil *et al.* (1987)	28	10	(36)	10	(36)
Avrahami *et al.* (1987)	18	4	(22)	3	(17)
Grant *et al.* (1987)	12	7	(58)	4	(33)
Kuzniecky *et al.* (1987)	40	26	(65)	21	(52)
Stefan *et al.* (1987)	10	8	(80)	4	(40)
Franceschi *et al.* (1989)	40	19	(48)	7	(18)
Convers *et al.* (1990)	63	23	(36)	13	(21)
Heinz *et al.* (1990)	39	27	(69)	19	(49)
Total	358	160	(45)	101	(28)

operated epileptic patients with histologically proven gliosis in the resected tissue (*see* Table 2 for a review). Overall, the relationship between hyperintense T_2-weighted images and the functional and lesional processes involved in focal epileptogenesis is not established firmly enough to rely on this type of MRI abnormality in the pre-surgical evaluation of epileptic patients, even when combined clinical MRI and EEG data indicate the most probable anatomical location of the epileptic focus.

TABLE 2 HISTOLOGICALLY PROVEN GLIOSIS ASSOCIATED WITH NORMAL MRI

	Gliosis on the resected epileptic tissue		
	Cases studied	*Normal MRI*	
Authors	*No*	*No.*	*%*
McLachlan *et al.* (1985)	8	4	(50)
Latack *et al.* (1986)	3	1	(33)
Lesser *et al.* (1986)	8	5	(62)
Sperling *et al* (1986)	18	18	(100)
Grant *et al.* (1987)	3	0	(0)
Kuzniecky *et al.* (1987)	26	11	(42)
Rougier *et al.* (1988)	6	2	(33)
Barbaro *et al.* (1989)	38	18	(48)
Hanson *et al.* (1989)	12	7	(58)
Jackson *et al* (1990)	27	2	(7)
Heinz *et al* (1990)	12	5	(42)
Sackellares *et al.* (1990)*	6	2	(33)
Theodore *et al.* (1990)*	11	8	(73)
Valk *et al.* (1990)	10	4	(40)
Total	188	87	(46)

*Cases with minimal gliosis were not considered here.

This issue can be addressed by studying the haemodynamic and metabolic patterns associated with hyperintense T_2-weighted image. Several studies have compared MRI and PET results in partial epilepsy (Latack *et al.*, 1986; Sperling *et al.*, 1986; Theodore *et al.*, 1986; Abou-Khalil *et al.*, 1987; Stefan *et al.*, 1987). However, these authors concentrated on the sensitivity and the topographic concordance of both methods, and did not look specifically for the degree of interictal focal hypometabolism indicated by the MRI result. In a previous study we investigated the relationship of hyperintense T_2-weighted images to regional Cerebral Blood Flow (rCBF) using SPECT and 99Tc-HMPAO (Ryvlin *et al.*, 1991). Hypoperfusion at the site of the EEG focus was found to be more frequent and more important in TLE patients with an abnormal MRI than in those whose MRI was normal. In the present work, we studied the cerebral metabolic patterns associated with hyperintense T_2-weighted image using Positron Emission Tomography (PET) and ^{18}F-fluorodeoxyglucose (^{18}FDG), and looked for a correlation between the presence of this non-specific MRI abnormality and the degree of focal hypometabolism.

METHODS

Patients

Clinical data are summarized in Table 3. We selected 19 patients suffering from refractory TLE. All had: (1) clinical evidence of complex partial seizures of temporal lobe origin based on the ictal symptoms (Bancaud, 1987); (2) a seizure frequency greater than 1 per month despite adequate drug therapy controlled by drug blood levels in the therapeutic range; (3) a unilateral temporal scalp EEG focus, assessed on several recordings repeatedly, showing focal slow waves in all patients with epileptiform abnormalities in 17 (89%) [interictal spikes or spike wave complexes in 16 (84%) and ictal discharges in 11 (58%)]; (4) a normal CT scan performed within the year preceding MRI, using a second generation device with and without contrast enhancement. MRI displayed hyperintense T_2-weighted image in the epileptogenic temporal lobe in 8 patients (Group I) and was normal in the remaining 11 (Group II). MRI techniques and data will be detailed later.

Patients were selected so that the 2 groups did not differ significantly with regard to age, gender, patient history (presence or absence of childhood convulsion or perinatal anoxia), side of the EEG focus, seizure frequency, and duration of epilepsy. There were 4 males and 4 females, age range 14−59 yrs (mean age SD = 27 ± 14) in Group I, and 5 males and 6 females, age range 21−59 yrs (mean SD = 35 ± 12) in Group II. Three patients of Group I (37%) and 5 patients of Group II (45%) had a past history of perinatal anoxia or infantile convulsions. Mean duration of epilepsy was 18 ± 15 yrs (3−55) in Group I and 16 ± 7 yrs (5−25) in Group II. Seizure frequency was classified in 3 categories, i.e. 1−5 per mth; 6−10 per mth; >10 per mth: and the distribution of seizure frequency was 5−1−2 (63%−12%−25%) and 7−1−3 (64%−9%−27%) in Groups I and II, respectively Patients with hyperintense T_2-weighted image on MRI were significantly younger at the onset of their epilepsy than those with a normal MRI (8.5 ± 10.6 yrs and 19.4 ± 13.4 yrs in Groups I and II, respectively, one-way t-test = $P < 0.05$). This difference was also observed in a larger group of 63 temporal lobe epileptics including the 19 cases of our series (unpublished data), and was taken into consideration in the statistical analysis. All patients were under medication with one or several major antiepileptic drugs [carbamazepine ($n = 14$), phenobarbital ($n = 12$), clobazam ($n = 8$), phenytoin ($n = 5$), valproic acid ($n = 3$), γ-vinyl GABA ($n = 2$)] with plasma levels of the drug in the therapeutic range on the day of the PET study. The temporal EEG focus was on the right side in 37% and 55% of the cases in Groups I and II, respectively.

Magnetic Resonance Imaging

MRI was performed at least twice in all cases. The first investigation was carried out within the 2 yrs preceding this study, and the second on the day of PET. Both MRI were performed using a 0.5 Tesla device with T_2-weighted images (TR 2000 ms, TE 60 and 120 ms) scanned in the axial plane; the first

TABLE 3 PATIENTS SUMMARY

Patient No.	Sex	Age (yrs)	Past history	Epilepsy		Seizures		EEG Abnormalities				Site of MRI abnormality
				Age of onset	*Duration*	*No /month*	*Symptoms*	*Slowing*	*Spikes*	*Discharges*	*Localization*	
Hyperintense T_2-weighted image signal on MRI												
1	M	20	—	6	14	1–5	LA, G, V, M	+	+	+	LT	LT
2	F	59	—	4	55	1–5	LA, G	+	+	−	RT	RT
3	F	20	P.Nat Anox	2	18	>10	LA, O, M, H	+	+	+	RT	RT
4	M	21	Inf Conv.	4	17	1–5	LA, O	+	+	+	LT	LT
5	F	21	—	6	15	1–5	LA, O, V	+	+	+	RT	RT
6	M	25	—	10	15	1–5	LA, O, A	+	+	−	LT	LT
7	M	14	Inf. Conv	2	12	6–10	LA, G, V	+	+	−	LT	LT
8	F	37	—	34	3	>10	LA, G	+	+	+	LT	LT
Normal MRI												
9	M	46	—	25	21	1–5	LA, G, H	+	−	+	LT	—
10	M	52	—	37	15	1–5	LA, O	+	+	+	RT	—
11	F	37	P.Nat. Anox	12	25	>10	LA, G, O	+	+	+	RT	—
12	F	27	—	2	25	1–5	LA, G, O	+	+	+	RT	—
13	F	28	—	10	18	1–5	LA	+	+	−	LT	—
14	M	35	—	27	8	>10	LA, O	+	+	+	LT	—
15	F	29	Inf Conv.	11	18	>10	LA, O	+	+	−	RT	—
16	M	59	—	47	12	1–5	LA, G, H	+	+	+	LT	—
17	F	22	Inf. Conv.	16	6	1–5	LA, G, O	+	+	−	LT	—
18	M	21	P.Nat. Anox.	16	5	1–5	LA, H	+	+	−	RT	—
19	F	29	Inf. Conv.	10	19	6–10	LA, V, H	+	+	+	RT	—

P.Nat. Anox = peri-natal anoxia, Inf. Conv. = infantile convulsion, LA = loss of awareness, G = gesture, V = vegetative disorder, M = partial tonic clonic motor symptom, O = oro-facial automatism, H = hallucination, A = affective trouble. R = Right, L = Left, T = Temporal.

investigation also provided coronal T_2 and T_1-weighted images (TR 500 ms, TE 21 ms). The slices of the second MRI were performed in the same planes as for the PET study (9 mm thick spaced by 3 mm, parallel to the orbito-meatal plane). In all patients, the second MRI demonstrated identical findings to the first investigation.

Different patterns of hyperintense T_2-weighted image could be distinguished according to their aspect size and location. Cases 1 – 3 exhibited the largest MRI abnormality which covered the temporal pole and the anterior portion of the temporal lobe (Fig. 1A,B). This abnormal MR signal was heterogeneous and

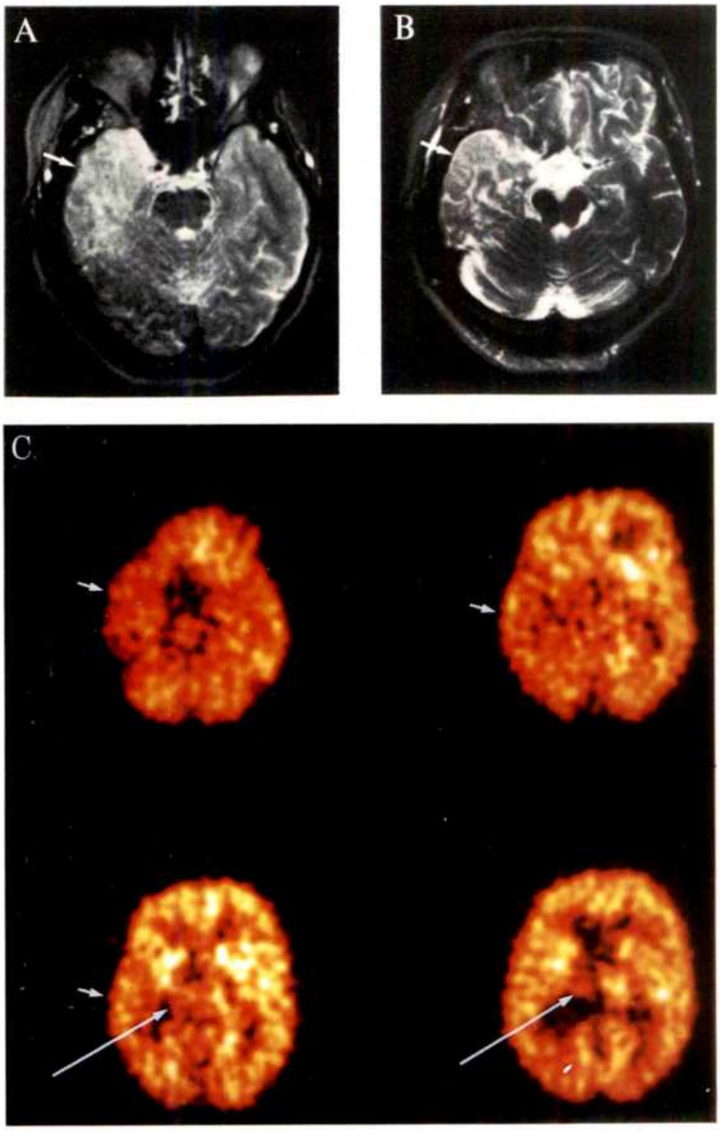

FIG. 1. Patient 2 with a right temporal EEG focus. A, B, axial T_2-weighted images (TR: 2000 ms, TE: 120 ms), from the first and second MRI studies, respectively, show a larger heterogeneous increased signal intensity in the anterior portion of the right temporal lobe (arrows). C, PET slices, comparable with those of the second MRI investigation, exhibited focal hypometabolism over the whole right lateral temporal cortex and over the right thalamus (arrows). All PET slices are displayed with a common scaling ranging from 0 to 9 mg/100 g/min.

resulted in a poor demarcation between grey and white matter. In Cases 4 and 5, the MRI abnormality had a similar aspect but was limited to the temporal pole (Fig. 2A,B). In Cases 6–8, the hyperintense T_2-weighted image was restricted to the mesial temporal grey matter (Figs 3, 4A,B).

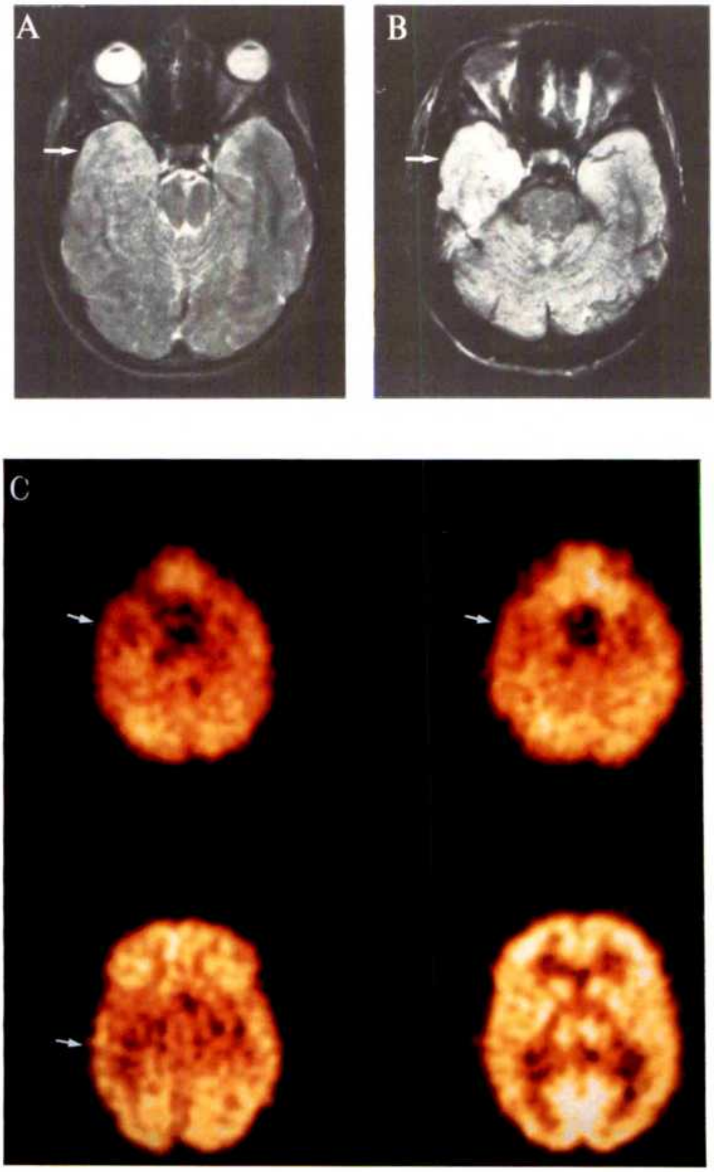

FIG. 2. Patient 5 with a right temporal EEG focus. A, B, axial T_2-weighted images (TR: 2000 ms, TE: 120 ms), from the first and second MRI studies, respectively, exhibited an heterogeneous hyperintense signal in the right temporal pole (arrows). C, PET slices, comparable with those of the second MRI investigation, showed evidence of focal hypometabolism over the anterior two-thirds of the right lateral temporal cortex (arrows). All PET slices are displayed with a common scaling ranging from 0 to 11 mg/100 g/min.

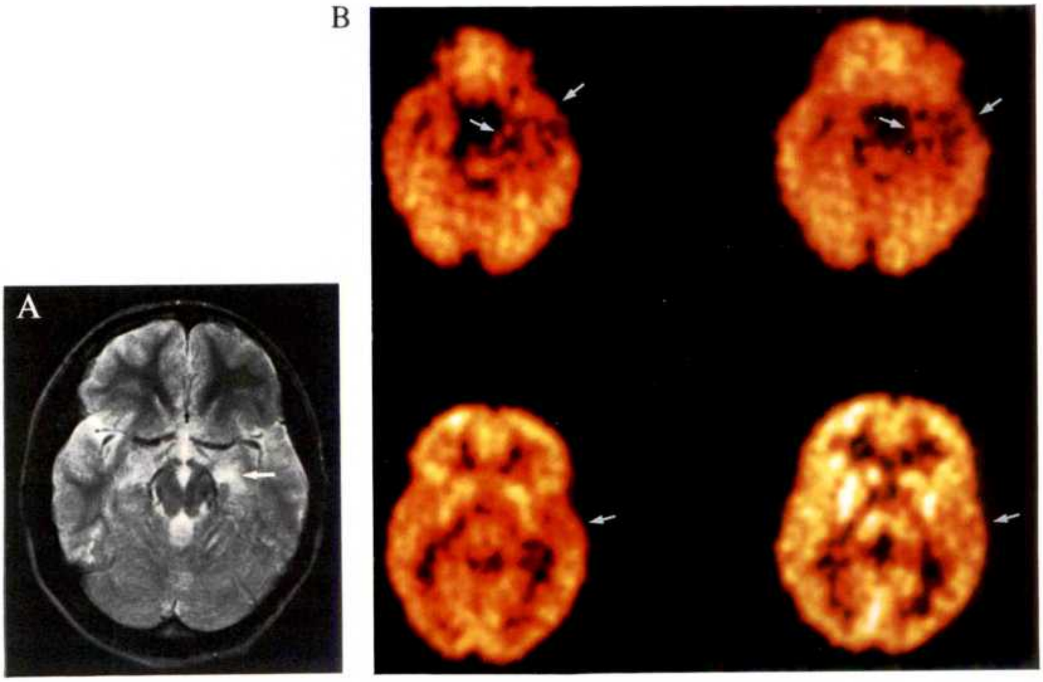

FIG. 3. Patient 7 with a left temporal EEG focus. A, orbito-meatal T_2-weighted MRI (TR: 2000 ms, TE: 120 ms) exhibits a small hyperintense signal restricted to the left mesial temporal cortex (arrow). B, comparable PET slices show focal hypometabolism over the left mesial temporal structures and the anterior half of the left lateral temporal cortex (arrows). All PET slices are displayed with a common scaling ranging from 0 to 13 mg/100 mg/min.

PET data acquisition

PET was carried out using a 'time of flight' scanner which simultaneously produces sets of seven 9 mm thick slices, spaced by 3 mm, with a spatial resolution of 7 mm. Patients were given 5 – 10 mCi of ^{18}FDG intravenously while lying with eyes closed and ears plugged. Arterial blood was sampled through a radial catheter every 2.5 min during the first 90 min following injection, and then at longer intervals. Two successive sets of 20 min scanning were started 40 min after ^{18}FDG injection. Both sets produced 7 axial slices parallel to the orbito-meatal plane (OM), with the lowest slice of each set placed at OM + 18 mm and OM + 24 mm, respectively. Attenuation was measured prior to ^{18}FDG injection by scanning 2 sets of slices similar to those described above, using a Germanium (^{68}Ge) rotative source. The local Cerebral Metabolic Rate of glucose (lCMRglc) was calculated according to Sokoloff's model (Sokoloff *et al.*, 1977) as modified by Phelps *et al.* (1979). We recorded the scalp-EEG activity for the 20 h preceding, and throughout the PET study. Eight Ag/AgCl cup electrodes filled with a conducting paste and attached with collodion, were placed at the sites of the international 10/20 system, and EEG was recorded using a 8-channel bipolar montage (F3-C3, C3-T3, T3-O1, F4-C4, C4-T4, T4-O2, Fz-Cz, Cz-Pz). Results were reported by an electroencephalographer blinded to the other data.

Patient 8 underwent 2 PET studies due to the fact that the first investigation was ictal. To ensure an interictal state during the second PET study a daily oral dose of 60 mg of clobazam was given the day preceding PET, and 5 mg of diazepam were infused intravenously during 1 h preceding and 1 h following the injection of ^{18}FDG. For this second investigation, 4 sets of 7 slices were scanned, 2 in the same orbito-meatal plane as the first PET, and 2 in a plane parallel to the longitudinal axis of the hippocampus.

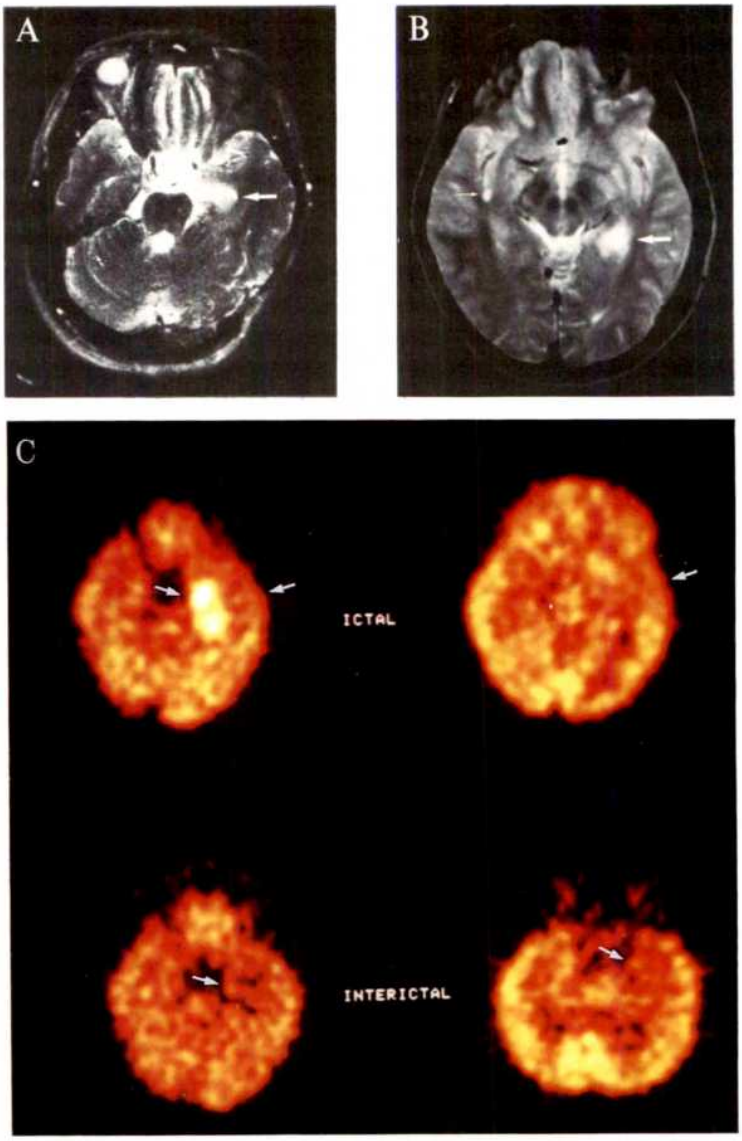

FIG. 4. Patient 8 with a left temporal EEG focus. A, B, axial T_2-weighted images (TR: 2000 ms, TE: 120 ms), from the second and third MRI, respectively, show increased signal intensity in the left mesial temporal cortex (arrows). A smaller hyperintense T_2-weighted image is also seen in the middle aspect of the right temporal lobe (small arrow). C, ictal PET images, in the same plane as that of the second MRI investigation, exhibited mesial temporal hypermetabolism (*upper left*), which fits remarkably with the site and size of the hyperintense signal, associated with left lateral temporal hypometabolism (*upper right*). In the interictal state, the hypermetabolic area became hypometabolic (*lower left*), which was better demonstrated on slices parallel to the longitudinal axis of the hippocampus (*lower right*). All PET slices are displayed with a common scaling ranging from 0 to 15 mg/100 g/min.

PET data analysis

We detected dysmetabolic areas, and compared their location with that of the hyperintense T_2-weighted image by visual analysis. Adequate comparison was made possible as both investigations were performed in succession, within 24 h, using the same tomographic parameters. Detection of PET abnormalities was assessed by 2 examiners, one of whom was blinded to clinical and MRI data.

We used quantitative data to look for a difference in metabolic activity between Groups I and II. PET data were analysed using circular Regions Of Interest (ROIs) of 10 mm diameter, placed on cortical and subcortical areas regardless to the site of dysmetabolism. Approximately 350 circular ROIs were drawn per patient, and lCMRglc was calculated for each of them. ROIs metabolic values were then pooled to assess the regional lCMRglc in the temporal, frontal, parietal and occipital lobes, and in the cerebellum. Caudate, putamen and thalamic nuclei lCMRglc were evaluated using the highest ROIs value in order to minimize partial volume effect. In 11 of the 19 patients, mesial temporal cortices were not delineated enough on PET images for a visual analysis of the metabolic activity (*see* Table 4), thus precluding a reliable placement of ROIs; consequently, we did not study quantitatively the metabolic rates in this region.

A regional asymmetry index (rAI) of metabolic activity between the 2 hemispheres expressed in percent was computed as follows: $rAI = 100^*(C-I)/[(C+I)/2]$ where C and I correspond to the lCMRglc in homotopic regions, respectively, contralateral and ipsilateral to the EEG focus. The maximal metabolic asymmetry (mAI) between 2 homotopic circular ROIs was similarly assessed in the temporal regions.

Statistical analysis

We looked for a relation between the abnormal MR signal and the metabolic asymmetry index using linear regression statistics [ANOVA (F-test) and β-coefficient table (two-tailed t test)].

RESULTS

EEG monitoring

EEG did not detect any ictal or post-ictal activity for the 45 min following ^{18}FDG injection in 19 of the 20 PET studies. During the first investigation of patient 8, 8 electrographic seizures were recorded, 2 with a mean duration of 1 min 10 s during the 10 first min following ^{18}FDG injection and 6 during the subsequent 35 min. No clinical seizures were noticed by the medical staff or by the patient herself during the PET. The patient was lying under the scanner with her face covered by a mask. Onset of discharges was recorded at the left temporal scalp electrode, which corresponded to the side of previous EEG and MRI abnormalities; the EEG discharges secondarily spread to the whole left hemisphere and the contralateral temporal lobe. Conversely, the EEG exhibited an interictal state throughout the second PET study of this patient. However, 6 left temporal EEG discharges similar to those described above were recorded during the preceding night.

Seven of the 18 other patients (Cases 1, 5, 7, 11, 12, 18, 19) exhibited ictal discharges during the 20 h preceding PET. However, none of these discharges occurred within the hour preceding the ^{18}FDG injection, and the EEG activity had always returned to the pre-discharge baseline at the time of injection.

Over the 24 h of monitoring, 17 of the 19 patients exhibited interictal EEG abnormalities confirming the site of previously established EEG focus. Only 2 patients had 24 h of normal EEG activity.

PET visual analysis

Results are summarized in Table 4. Of the 19 patients who underwent an interictal PET study, 16 (84%) exhibited focal hypometabolism. In all of these 16 abnormal PET studies but one (patient 12), the relative hypometabolism affected, exclusively or predominantly, the temporal lobe where the EEG abnormalities had been observed.

TABLE 4. PET RESULTS VISUAL ANALYSIS

Patient	*Temporal*		*Extra-temporal hypometabolism*
	Lateral hypometabolism	*Mesial dysmetabolism*	
Hyperintense T_2-weighted image on MRI			
1	> anterior 1/3	?	Centro-parietal
2	> anterior 1/3	?	Thalamic
3	> anterior 1/3	?	Frontal + parietal
4	> anterior 1/3	?	—
5	> anterior 1/3	?	—
6	> anterior 1/3	Hypometabolism	Centro-parietal
7	> anterior 1/3	Hypometabolism	—
8 ictal	> anterior 1/3	Hypometabolism	—
8 interictal	> anterior 1/3	Hypometabolism	—
Normal MRI			
9	> anterior 1/3	Hypometabolism	Centro-parietal
10	< anterior 1/3	?	—
11	< anterior 1/3	?	—
12	< anterior 1/3	—	—
13	< anterior 1/3	—	—
14	—	?	—
15	< anterior 1/3	Hypometabolism	—
16	—	?	—
17	—	?	—
18	< anterior 1/3	—	—
19	> anterior 1/3	?	Centro-parietal

> anterior 1/3 = lateral temporal hypometabolism extending beyond the anterior third of the lateral temporal cortex; < anterior 1/3 = lateral temporal hypometabolism retained within the anterior third of the lateral temporal cortex; ? = mesial temporal cortex poorly delineated bilaterally

Patient 12, whose MRI was normal, showed a right temporal EEG focus while PET showed evidence of focal hypometabolism in the left temporal lobe.

The 16 patients with interictal focal hypometabolism included all of those with an hyperintense T_2-weighted image (Group I) and 8 of the 11 whose MRI was normal (Group II). Hypometabolism showed different patterns of extension in the 2 groups.

Patients with hyperintense T_2-weighted image on MRI

In all patients with an abnormal MRI, the interictal hypometabolic area encompassed the abnormal MR signal, and extended beyond the anterior third of the lateral temporal cortex. In patients 1–3 who showed the largest hyperintense T_2-weighted image, the whole corresponding temporal lobe was hypometabolic (Fig. 1c). However, it was not possible to estimate the involvement of the mesial temporal cortex which was poorly delineated bilaterally in these cases. These 3 patients also exhibited ipsilateral extra-temporal hypometabolism affecting the centro-parietal region in one case (1), the thalamus in another (2), and the frontal and parietal lobes in the last one (3). Patient 2 was the only case with visually detectable subcortical hypometabolism (Fig. 1c). Cases 4 and 5, who showed a hyperintense T_2-weighted image limited to the temporal pole, had a hypometabolic area expanding to the anterior two-thirds of the lateral temporal cortex (Fig. 2c). Cases 6, 7 and 8, who showed an abnormal mesial temporal MR signal, also exhibited a large hypometabolic area which involved the mesial temporal region and the anterior half or two-thirds of the lateral temporal cortex (Fig. 3B). The ipsilateral centro-parietal region was also involved in Case 7. Patient 8 also had an ictal PET showing focal hypermetabolism in the left mesial temporal region ipsilateral to the EEG temporal discharges (Fig. 4C). The hypermetabolic area was hypometabolic interictally, and matched remarkably the topography of the MRI abnormality. Concomitantly, the ictal PET displayed focal hypometabolism over the anterior part of the left lateral temporal cortex.

Patients with a normal MRI

In 3 of the 11 patients with a normal MRI, no focal hypometabolism could be detected. In 6 of the 8 remaining patients, the hypometabolic area was limited to the temporal pole and to the anterior third of the lateral temporal cortex on orbito-meatal slices. Finally, only 2 patients with a normal MRI (9 and 19) displayed a large abnormality on orbito-meatal slices, involving the anterior two-thirds of the lateral temporal cortex, the mesial temporal cortex, and the ipsilateral centro-parietal region in one case (9) and the whole temporal lobe and the ipsilateral centro-parietal region in the other (19).

PET quantitative data

LCMRglc data are summarized in Table 5. Asymmetry index (AI) data are shown in Table 6 and Fig. 5.

Asymmetry index in the temporal lobe

In all patients with a hyperintense T_2-weighted image, the temporal lobe where EEG and MRI abnormalities had been found also exhibited lower lCMRglc than contralaterally. In all but 2 of the patients (12 and 15) with a normal MRI, the temporal lobe ipsilateral to the EEG focus also exhibited the lowest temporal lCMRglc. Patient 12 with focal hypometabolism contralateral to the EEG focus at the first investigation, had accordingly negative regional (r) and maximal (m) asymmetry index in the temporal lobe (rAI = −7%, mAI = −34%). In patient 15, visual analysis detected a small area of hypometabolism in the anterior part of the right temporal lobe, ipsilateral to the EEG focus, where the metabolic rate was decreased by 27% (mAI = 27%); however, the regional lCMRglc was slightly higher in this lobe than contralaterally (rAI = −3%).

The 2 homotopic circular ROIs which displayed the maximal AI in the temporal lobes were located in the temporal pole in 6 patients, in the anterior half of the lateral temporal cortex in 11 and in its posterior half in 2. In the 5 patients whose hyperintense T_2-weighted image extended to the lateral temporal cortex, the maximal AI was observed in the area of the abnormal MR signal. This topographic concordance could not be assessed in patients whose MRI abnormality was restricted to the mesial temporal cortex since no ROI was placed in that region when analysing PET data (*see* Methods).

Statistical analysis

Patient 12 was excluded from statistical analysis because the conflicting lateralization provided by EEG and PET data in this case resulted in meaningless negative asymmetry index. Excluding this patient did not alter the matching between Groups I (abnormal MRI) and II (normal MRI) with regard to age, gender, patient history, side of the EEG focus, seizure frequency and duration of epilepsy.

TABLE 5. PET RESULTS LOCAL CEREBRAL METABOLIC RATES OF GLUCOSE

	Temporal		*Frontal*		*Parietal*		*Occipital*		*Cerebellum*		*Caudate*		*Putamen*		*Thalamus*	
Patient	*(F)*	*(N)*	*(F)*	*(N)*	*(F)*	*(N)*	*(F)*	*(N)*	*(F)*	*(N)*	*(F)*	*(N)*	*(F)*	*(N)*	*(F)*	*(N)*
Hyperintense T_2-weighted image on MRI																
1	3.9	4.9	5.7	5.6	5.6	6.4	4.8	5.3	2.8	3.1	7.0	8.0	7.2	8.0	7.5	6.8
2	4.1	5.1	5.6	5.8	4.9	4.9	4.7	4.7	4.7	4.3	6.6	7.9	7.2	8.9	4.3	6.7
3	6.7	8.2	10.5	14.0	7.2	9.0	5.8	5.5	5.6	4.9	11.6	11.3	12.3	13.3	11.4	11.0
4	5.4	7.2	8.1	8.3	6.8	7.4	7.4	7.4	6.4	7.0	7.5	7.8	9.3	9.1	9.3	8.7
5	6.5	7.0	9.0	8.9	8.8	8.9	8.4	8.4	7.8	7.3	9.3	9.4	10.9	10.0	9.6	10.2
6	7.5	9.3	10.6	10.9	10.2	11.0	8.1	8.0	7.6	7.1	13.4	13.3	13.2	13.8	13.0	13.1
7	6.9	8.0	9.4	10.1	8.5	9.3	8.6	8.5	6.8	7.0	10.9	10.8	12.5	12.9	10.5	10.8
8 ictal	8.2	9.1	9.2	10.1	9.3	11.1	8.1	8.4	8.7	8.8	10.8	11.1	10.8	10.7	12.0	12.9
8 interictal	7.5	8.1	8.5	8.8	8.2	9.4	7.2	7.4	7.3	8.0	9.0	9.5	10.1	11.7	11.1	11.1
Normal MRI																
10	6.0	6.6	7.2	7.3	7.5	7.7	6.9	6.5	5.0	4.9	8.9	9.3	8.9	9.3	7.1	8.6
11	7.3	7.4	8.8	8.8	8.4	8.3	8.8	8.4	7.0	6.1	12.9	12.0	11.1	13.6	13.9	12.3
12	6.3	6.7	8.5	8.2	7.9	8.0	7.3	7.4	4.8	5.3	9.9	9.5	9.8	10.8	9.3	10.0
13	5.9	5.5	7.2	7.0	6.7	6.5	6.2	6.6	7.1	7.3	8.4	9.1	9.7	9.5	9.5	8.2
14	7.9	8.1	8.6	9.8	9.1	9.5	7.7	7.7	9.1	7.9	10.5	11.5	13.1	13.8	10.0	11.2
15	6.3	6.5	7.5	7.5	7.2	7.7	6.9	6.4	4.9	5.0	8.3	8.8	9.5	10.7	8.8	9.5
16	7.3	7.1	8.9	8.7	8.7	7.9	7.4	6.8	7.5	7.0	10.6	10.2	11.0	11.5	10.4	10.4
17	4.6	4.9	4.9	5.0	5.0	5.3	5.2	5.5	4.8	5.2	6.5	6.6	7.1	7.9	6.1	5.9
18	5.7	6.2	7.8	7.5	6.2	6.8	5.9	6.1	4.1	4.3	8.7	9.2	9.1	9.3	8.7	9.1
19	7.2	7.4	8.9	8.5	8.5	8.1	7.4	6.9	8.5	7.7	10.1	9.5	10.9	11.2	11.7	11.4
20	5.6	6.9	8.2	8.4	7.7	8.4	6.8	6.8	5.9	6.4	8.5	8.6	9.0	8.8	8.9	9.9

F (focus) = side of the EEG focus, N (normal) = side controlateral to the EEG focus. All values correspond to Local Cerebral Metabolic Rates of glucose (LCMRglc) and are expressed in mg/100 of tissue/min.

TABLE 6 PET RESULTS—ASYMMETRY INDEX

Patient	*Temporal*		*Frontal*	*Parietal*	*Occipital*	*Cerebellum*	*Caudate*	*Putamen*	*Thalamus*
	Regional	*Maximal*							
Hyperintense T_2-weighted image on MRI									
1	23	46	−1	13	11	7	13	10	−10
2	21	68	2	0	0	−9	18	21	44
3	20	53	28	23	−6	−14	−2	8	−3
4	29	72	2	8	−1	9	3	−2	−6
5	7	37	−1	1	1	−6	1	−9	5
6	22	62	4	8	−2	−8	−1	5	1
7	14	69	7	10	−1	3	−1	3	3
8 ictal	10	30	9	17	3	2	4	−1	7
8 interictal	8	34	3	15	3	9	6	14	0
Normal MRI									
9	9	26	2	3	−6	−1	4	5	20
10	1	25	0	−1	−5	−14	−7	20	−12
11	6	26	−4	1	0	9	−4	10	7
12	−7	−34	−3	−3	5	3	8	−2	−20
13	2	38	3	4	0	−14	9	5	12
14	2	16	1	7	−7	2	5	11	9
15	−3	27	−2	−10	−9	−7	−4	5	0
16	6	27	3	7	5	8	1	11	−3
17	9	19	−4	9	3	4	5	3	4
18	4	37	−4	−5	−6	−10	−6	3	−2
19	21	62	3	9	0	9	1	−3	11

All values are expressed in percent and calculated as: $100*(C-I)/[(C+I)/2]$ with C and I corresponding to the lCMRglc in homotopic regions controlateral and ipsilateral to the EEG focus, respectively.

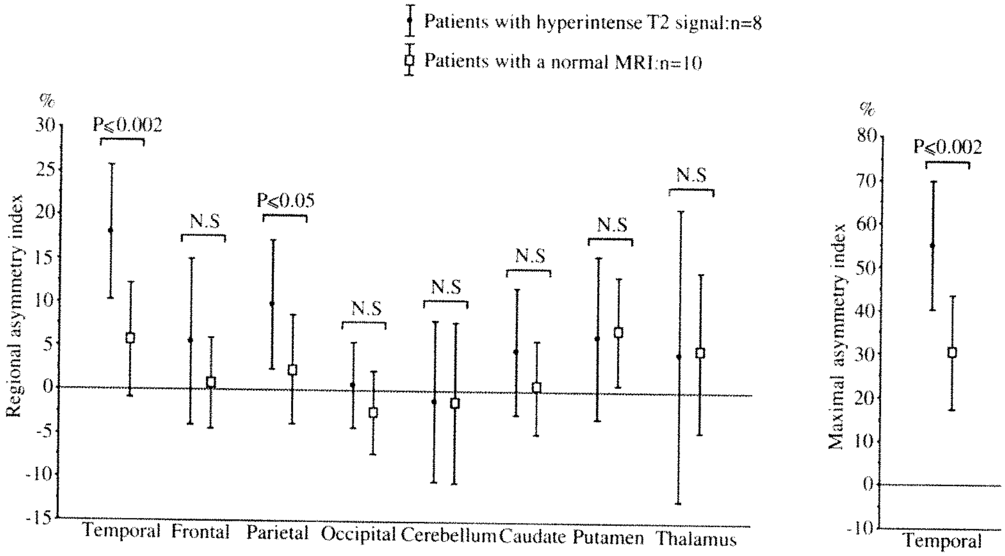

FIG. 5. Comparison of the regional and maximal asymmetry index between Groups I and II.

The regional as well as the maximal AI in the temporal lobes were significantly related to the presence of an abnormal MRI image ($P \leq 0.002$). Patients with hyperintense T_2-weighted image had higher AI than patients with a normal MRI. The same trend, although less marked, was observed for the parietal lobes ($P < 0.05$). There was no significant relation between regional AI and MRI data in the 6 other regions studied. The regional and the maximal AI in the temporal lobes were also found to be related to the age of onset of epilepsy ($P < 0.05$ and $P < 0.01$, respectively); the younger the age of onset, the higher the AI. This was not the case for parietal AI. When multiple regression analysis was performed to eliminate the potentially confusing effect of age of onset, the relation between the presence of a hyperintense T_2-weighted image and the temporal AI remained significant ($P \leq 0.02$).

Ictal case (8)

In patient 8, ictal lCMRglc was 15 mg/100 g/min in the 'hypermetabolic area', while the mean cortical lCMRglc was 9.2 mg/100 g/min, indicating that the relative hypermetabolism detected on visual analysis corresponded to an absolute increase in glucose consumption. Furthermore, interictal lCMRglc was 4.6 mg/100 g/min in the same zone, corresponding to a more than threefold decrease compared with the ictal value. All cortical and subcortical structures also exhibited lower lCMRglc at the second investigation. Decrease of regional lCMRglc ranged from 4% (left thalamus) to 18% (right parietal), and was 12% for the mean cortical lCMRglc. The regional and maximal AI in the temporal lobes were slightly modified at the second PET study as compared with the first one (rAI: 10% and 8%, mAI: 30% and 34% at the first and second investigation, respectively) indicating that the relative left lateral temporal hypometabolism did not differ significantly between the ictal and interictal states.

DISCUSSION

PET sensitivity

PET-detected focal hypometabolism in 73% of patients with a normal MRI and in all patients whose MRI was abnormal, resulting in an overall sensitivity of 84%. This sensitivity of PET was comparable and even slightly better than that reported earlier in a large series of temporal lobe epileptics investigated with PET ^{18}FDG but not with MRI (Kuhl *et al.*, 1980; Engel *et al.*, 1982*a*; Theodore *et al.*, 1983). Focal hypometabolism affected the temporal lobe exclusively or predominantly in all cases, and extended to ipsilateral extratemporal regions in 7. This concerned the centro-parietal region in 4 patients, including 2 whose MRI was normal (1, 6, 9, 19), and the whole fronto-parietal structures in 1 (3). Only 1 patient whose MRI was abnormal exhibited subcortical hypometabolism affecting the thalamus. This latter result contrasts with those of other series which reported 30–44% of lateralized subcortical hypometabolism ipsilateral to the EEG focus, and most frequently affecting the caudate (Sperling *et al.*, 1990) or the thalamus (Henry *et al.*, 1989). The small size of subcortical structures compared with the resolution of PET makes it difficult to assess the metabolic activity of these nuclei in a reliable fashion. The better resolution of our PET device (7×7×9 mm) compared with that used by Sperling *et al.* (1990) (16.5×16.5×17.5 mm), largely decreases the spill-over effect which spreads cortical hypometabolism on to subcortical structures. Moreover, the important spatial sampling of our data might help to distinguish subcortical metabolic asymmetry due to a misposition of the patient's head in the scanner from authentic lateralized subcortical hypometabolism. Both of these characteristics might explain why subcortical abnormalities were more frequent in other reports than in ours. Conversely, it might be that our visual criteria for subcortical asymmetry is less sensitive than those of other investigators, and underestimates the rate of true subcortical hypometabolism. Indeed, subcortical nuclei associated with an AI up to 21% were not considered hypometabolic according to visual analysis.

PET lateralization with regard to the EEG focus

PET and scalp EEG data were discordant in only 1 of our cases (12) whose MRI was normal; metabolic and EEG abnormalities were left and right temporal, respectively. Other cases have been reported with focal hypometabolism contralateral to the scalp EEG focus (Engel *et al.*, 1982*c*), raising the question of which of these 2 abnormalities is the most reliable. Comparing scalp-sphenoidal ictal EEG PET and stereo electroencephalography (SEEG) data in 153 patients, Engel *et al.* (1990) found that scalp-sphenoidal EEG ictal onsets could result in false lateralization with regard to the SEEG abnormalities and to the surgical outcome. Conversely, focal hypometabolism was never contralateral to the SEEG focus except in 2 patients with artifactual PET abnormalities related to depth electrodes implantation.

PET sensitivity and lateralization with regard to hyperintense T_2-weighted images

In patients with hyperintense T_2-weighted image, PET sensitivity was 100%, and focal hypometabolism was always ipsilateral to the MRI abnormality and to the EEG focus. These results are in agreement with most of the studies comparing MRI and PET in partial epilepsy (Latack *et al.*, 1986; Abou-Khalil *et al.*, 1987; Stefan *et al.*, 1987;

Theodore *et al.*, 1990). In contrast, Sperling *et al.* (1986) reported a complete discordance between both investigations. In his series, the 3 patients with abnormal MRI who underwent PET, including 1 with histologically proven tumour, exhibited normal cerebral metabolism, while MRI was normal in the 12 cases with focal hypometabolism, including 10 with mesial temporal sclerosis. The authors concluded that in their series, MRI mainly detected non-sclerotic epileptogenic lesions that might be less visible with PET; as a matter of fact, PET was proved less sensitive than MRI in detection of epileptogenic tumour (Henry *et al.*, 1987; Hanson *et al.*, 1989; Theodore *et al.*, 1990). Thus, the discrepancy between Sperling's and others' data might be due primarily to a difference in the type of pathological finding detected by MRI, namely sclerotic or non-sclerotic. Indeed, most of the series reported gliosis as the most common pathological finding associated with non-specific hyperintense T_2-weighted image in TLE (McLachlan *et al.*, 1985; Grant *et al.*, 1987; Kuzniecky *et al.*, 1987; Jackson *et al.*, 1990), and all patients showing this association also exhibited focal hypometabolism when explored with PET (Latack *et al.*, 1986; Theodore *et al.*, 1990).

Correlation between the degree of hypometabolism and MRI data

The extension of temporal hypometabolism varies according to both the presence and the type of hyperintense T_2-weighted image. The hypometabolic area extended beyond the anterior third of the lateral cortex in all the patients with an abnormal MR signal but only in 2 of the 11 with a normal MRI (18%). Furthermore, the 3 patients with the largest hyperintense T_2-weighted image (1−3) also exhibited the largest hypometabolism, involving the whole temporal cortex. Quantitative analysis confirmed that the regional asymmetry index in the temporal lobes were significantly higher in patients with hyperintense T_2-weighted image than in patients with a normal MRI. This result is in accordance with the more important temporal hypoperfusion demonstrated by SPECT in TLE patients with hyperintense T_2-weighted image on MRI as compared with those whose MRI was normal (Ryvlin *et al.*, 1991). The maximal AI in the temporal lobes were also higher in patients with hyperintense T_2-weighted image, indicating that not only the extent, but also the intensity of hypometabolism was more important in these patients. Interestingly, the site of the abnormal MR signal was always metabolically impaired, and included the ROI exhibiting the maximal AI in the 5 patients whose hyperintense T_2 signal affected the lateral temporal cortex. Finally, although there was no significant difference in visually detected extratemporal hypometabolism between our 2 groups, quantitative analysis demonstrated that patients with hyperintense T_2-weighted image had significantly higher AI in the parietal lobes than those with a normal MRI.

Thus, all of the above data converge to support the conclusion that glucose metabolism in the epileptogenic temporal lobe, and at a lesser degree in the ipsilateral parietal lobe, is more depressed when MRI shows a non-specific hyperintense T_2-weighted image than when MRI is normal. This association proved to be independent of the clinical difference demonstrated between our 2 groups of patients (i.e. age of onset), while all the other clinical data, in particular those related to the severity of epilepsy, were matched between groups. Moreover, the degree of hypometabolism is known to be unrelated to the epileptogenic activity as measured by seizure or interictal spike frequency (Engel *et al.*, 1982*a*; Theodore *et al.*, 1983; Abou-Khalil *et al.*, 1987). Therefore, the more important hypometabolism observed in patients with hyperintense T_2-weighted image, as compared with those with a normal MRI, is likely to be directly related to the presence of the MRI abnormality.

Several authors have suggested that gliosis is responsible for non-specific hyperintense T_2 signal (Berkovic *et al.*, 1986; Jabbari *et al.*, 1986; Grant *et al.*, 1987; Theodore *et al.*, 1988; Triulzi *et al.*, 1988; Franceschi *et al.*, 1989; Heinz *et al.*, 1990). Kuzniecky *et al.* (1987) found this MRI abnormality to correlate with the intensity of temporal sclerosis. More recently, Jackson *et al.* (1990) reported a sensitivity of 93% and a specificity of 86% in the MRI assessment of hippocampal sclerosis; MRI diagnosis was based on the presence of hippocampal hyperintense T_2-weighted image associated with an asymmetric small hippocampus on T_1-weighted images. Temporal sclerosis was also found to be the most common pathological finding associated with focal hypometabolism in TLE (Engel *et al.*, 1982*b*; Sperling *et al.*, 1986; Theodore *et al.*, 1990), and this structural change is thought to be partly responsible for the metabolic disorder (Engel *et al.*, 1982*b*). Therefore, the more severe gliosis observed in patients with hyperintense T_2-weighted image (Kuzniecky *et al.*, 1987) might well account for the more important metabolic disturbances exhibited in those type of patients in our series. Indeed, this mechanism might apply not only at the lesional site, but also over its projection field, including the lateral temporal and parietal cortices. Consistent with the role of deafferentation is the finding that TLE patients with temporo-parietal hypometabolism on pre-operative PET exhibit unchanged parietal hypometabolism 1 yr after temporal lobectomy, while being seizure free (Hanson *et al.*, 1990).

However, some facts challenged the above hypothesis. The degree of hypometabolism was not found to correlate with that of mesial temporal neuronal loss (Henry *et al.*, 1988), nor with the overall lateral or mesial temporal histologic abnormalities (Radtke *et al.*, 1990; Sackellares *et al.*, 1990), contradicting previous results (Engel *et al.*, 1982*b*; Yamamoto *et al.*, 1983). Other findings do not support the gliotic origin of hyperintense T_2-weighted image: (1) numerous cases have been reported with gliosis in the resected epileptic tissue and a normal pre-operative MRI (*see* Table 2 for a review); (2) experimental gliosis induced by freezing did not result in abnormal MR signal on T_2-weighted images (Barnes *et al.*, 1988). Therefore, it might be that the more important hypometabolism demonstrated in patients with hyperintense T_2-weighted image, as compared with those whose MRI is normal, is not related to a lesional process. As a matter of fact, functional mechanisms could also participate in the pathophysiology of interictal focal hypometabolism (Engel *et al.*, 1982*b*), and these might underly the metabolic difference observed between our 2 groups. Increased binding of C11-carfentanil has been found to correlate with the degree of interictal hypometabolism in the lateral temporal cortex of TLE patients (Frost *et al.*, 1988), indicating that the functional processes responsible for hypometabolism might be related to changes in the μ-opiate receptors system. However, because these processes are not yet clearly identified, it remains difficult at the moment to draw firm conclusions about the relationship between hyperintense T_2-weighted image and the functional aspects of focal hypometabolism.

Ictal case (8)

The spatial concordance between PET and MRI data is also illustrated by patient 8 whose ictal PET showed evidence of focal hypermetabolism in the left mesial temporal lobe which matched remarkably the site of the hyperintense T_2-weighted image. This hypermetabolic area was coherent with the topography of EEG discharges, and proved to be hypometabolic in the interictal state, indicating that the hypermetabolic activity was seizure induced. A few ictal PET studies have been reported in the literature and have shown various metabolic patterns (Kuhl *et al.*, 1980; Engel *et al.*, 1983; Theodore *et al.*, 1983; Franck *et al.*, 1986; Abou-Khalil *et al.*, 1987; Stefan *et al.*, 1987). These consisted of focal hypermetabolism usually predominating at the site of the seizure focus, and occasionally associated with adjacent and/or remote hypometabolism. However, to our knowledge, focal hypermetabolism has never been found restricted to mesial temporal structures nor to fit precisely with the location of non-specific hyperintense T_2-weighted image ictal PET studies. Conversely, a recent post-ictal SPECT study in 32 patients with TLE reported relative mesial temporal hyperperfusion in 22 associated with ipsilateral lateral temporal hypoperfusion in 13 (Rowe *et al.*, 1989). Thus, the pattern observed in patient 8, comparable with that reported in the above series, might reflect the post-ictal more than the ictal state. As a matter of fact, the metabolic activity observed in our case reflects the mixed effect of both ictal and post-ictal phases with regard to the ^{18}FDG accumulation period (Sokoloff *et al.*, 1977).

Such precise topographic concordance was not demonstrated between the sites of hyperintense T_2-weighted image and ictal SEEG recordings (Rougier *et al.*, 1988). However, at present, topographic comparison might be more reliable between MRI and PET images using similar acquisition tomographic parameters, than between MRI and SEEG data when depth electrodes are implanted regardless of the MRI abnormalities; it is likely that MRI guided placement of depth electrodes will best address this issue in the future.

To conclude, this study supports the view that non-specific hyperintense T_2-weighted signals in temporal lobe epilepsy are likely to reflect an epileptogenic lesion when located in the same temporal lobe as the EEG focus. In such cases, the utility of demonstrating focal interictal metabolism using PET can reasonably be questioned since PET does not provide additional information regarding the site of the epileptogenic zone. Conversely, TLE patients with a normal MRI are likely to benefit from a PET study in the pre-surgical evaluation of their disease, the result of which might not necessarily agree with scalp-EEG data.

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REFERENCES

Abou-Khalil BW, Sackellares JC, Latack JT, Vanderzant CW (1984) Magnetic resonance imaging in refractory partial epilepsy. *Epilepsia*, **25**, 650.

Abou-Khalil BW, Siegel GJ, Sackellares JC, Gilman S, Hichwa R, Marshall R (1987) Positron emission tomography studies of cerebral glucose metabolism in chronic partial epilepsy. *Annals of Neurology*, **22**, 480–486.

AVRAHAMI E, COHN DF, NEUFELD M, FRISHMAN E, BENMAIR J, SCHREIBER R *et al.* (1987) Magnetic resonance imaging (MRI) in patients with complex partial seizures and normal computerized tomography (CT) scan *Clinical Neurology and Neurosurgery*, **89**, 231–235.

BANCAUD J (1987) Sémiologie clinique des crises épileptiques d'origine temporale *Revue Neurologique*, **143**, 392–400.

BARBARO NM, DILLON WP, DOWD CF, BLUESTONE DL, LAXER KD (1989) Magnetic resonance image evaluation of patients with pathologically proven mesial temporal sclerosis. *Epilepsia*, **30**, 711.

BARNES D, MCDONALD WI, LANDON DN, JOHNSON G (1988) The characterization of experimental gliosis by quantitative nuclear magnetic resonance imaging. *Brain*, **111**, 83–94.

BERGEN D, MORRELL F, BLECK T, RISTANOVIC R, RAMSEY R, WHISLER WW (1985) Tissue histology in epileptic patients with abnormal MRI scans. *Epilepsia*, **26**, 543–544.

BERKOVIC SF, ETHIER R, ROBITAILLE Y, OLIVIER A, FEINDEL W, MELANSON D *et al.* (1986) Magnetic resonance imaging of the hippocampus: II. Mesial temporal sclerosis. *Epilepsia*, **27**, 612.

CONVERS P, BIERME T, RYVLIN P, REVOL M, FISCHER C, FROMENT JC *et al.* (1990) Apport de l'imagerie par résonance magnétique dans 100 cas d'épilepsie partielle rebelle à scanner X normal. *Revue Neurologique*, **146**, 330–337.

ENGEL J, KUHL DE, PHELPS ME, MAZZIOTTA JC (1982*a*) Interictal cerebral glucose metabolism in partial epilepsy and its relation to EEG changes *Annals of Neurology*, **12**, 510–517.

ENGEL J, BROWN WJ, KUHL DE, PHELPS ME, MAZZIOTTA JC, CRANDALL PH (1982*b*) Pathological findings underlying focal temporal lobe hypometabolism in partial epilepsy. *Annals of Neurology*, **12**, 518–528.

ENGEL J, KUHL DE, PHELPS ME, CRANDALL PH (1982*c*) Comparative localization of epileptic foci in partial epilepsy by PCT and EEG. *Annals of Neurobiology*, **12**, 529–537.

ENGEL J, KUHL DE, PHELPS ME, RAUSCH R, NUWER M (1983) Local cerebral metabolism during partial seizures *Neurobiology, Cleveland*, **33**, 400–413.

ENGEL J, HENRY TR, RISINGER MW, MAZZIOTTA JC, SUTHERLING WW, LEVESQUE MF *et al* (1990) Presurgical evaluation for partial epilepsy: relative contributions of chronic depth-electrode recordings versus FDG-PET and scalp-sphenoidal ictal EEG. *Neurology, Cleveland*, **40**, 1670–1677.

FRANCESCHI M, TRIULZI F, FERINI-STRAMBI L, GIUSTI MC, MINICUCCI F, FAZIO F *et al.* (1989) Focal cerebral lesions found by magnetic resonance imaging in cryptogenic nonrefractory temporal lobe epilepsy patients. *Epilepsia*, **30**, 540–546.

FRANCK G, SADZOT B, SALMON E, DEPRESSEUX JC, GRISAR T, PETERS JM *et al.* (1986) Regional cerebral blood flow and metabolic rates in human focal epilepsy and status epilepticus. *Advances in Neurology*, **44**, 935–948

FROST JJ, MAYBERG HS, FISHER RS, DOUGLASS KH, DANNALS RF, LINKS JM *et al.* (1988) Mu-opiate receptors measured by positron emission tomography are increased in temporal lobe epilepsy. *Annals of Neurology*, **23**, 231–237.

GRANT R, HADLEY DM, CONDON B, DOYLE D, PATTERSON J, BONE I *et al.* (1987) Magnetic resonance imaging in the management of resistant focal epilepsy: pathological case report and experience of 12 cases. *Journal of Neurology, Neurosurgery, and Psychiatry*, **50**, 1529–1532.

HANSON MW, RADTKE RA, BOYKO OB, COLEMAN RE (1989) FDG-PET, MRI, and pathologic findings in patients with complex partial seizures. *Journal of Nuclear Medicine*, **30**, 752.

HANSON MW, HOFFMAN JM, RADTKE RA, COLEMAN RE (1990) FDG PET in the assessment of hypometabolism before and after temporal lobectomy in patients with seizures. *Journal of Nuclear Medicine*, **31**, 710–711

HEINZ ER, CRAIN BJ, RADTKE RA, BURGER PC, FRIEDMAN AH, DJANG WT *et al.* (1990) MR imaging in patients with temporal lobe seizures: correlation of results with pathologic findings. *AJNR: American Journal of Neuroradiology*, **11**, 827–832.

HENRY TR, ENGEL J, SUTHERLING WW, RISINGER MW, PHELPS ME (1987) Correlation of structural and metabolic imaging with electrographic localization and histopathology in refractory complex partial epilepsy. *Epilepsia*, **28**, 601.

HENRY TR, ENGEL J, BABB TL, PHELPS ME (1988) Correlation of neuronal cell loss with degree of interictal focal temporal hypometabolism in complex partial epilepsy. *Neurology, Cleveland*, **38**, Supplement 1, 156.

HENRY TR, ENGEL J, PHELPS ME (1989) Subcortical hypometabolism on interictal PET in complex partial seizures. *Neurology, Cleveland*, **39**, Supplement 1, 299.

Jabbari B, Gunderson CH, Wippold F, Citrin C, Sherman J, Bartoszek D *et al.* (1986) Magnetic resonance imaging in partial complex epilepsy. *Archives of Neurology, Chicago,* **43**, 869–872.

Jackson GD, Berkovic SF, Tress BM, Kalnins RM, Fabinyi GCA, Bladin PF (1990) Hippocampal sclerosis can be reliably detected by magnetic resonance imaging. *Neurology, Cleveland,* **40**, 1869–1875.

Kuhl DE, Engel J, Phelps ME, Selin C (1980) Epileptic patterns of local cerebral metabolism and perfusion in humans determined by emission computed tomography of ^{18}FDG and ^{13}NH$_3$. *Annals of Neurology,* **8**, 348–360.

Kuzniecky R, de la Sayette V, Ethier R, Melanson D, Andermann F, Berkovic S *et al.* (1987) Magnetic resonance imaging in temporal lobe epilepsy: pathological correlations. *Annals of Neurology,* **22**, 341–347.

Latack JT, Abou-Khalil BW, Siegel GJ, Sackellares JC, Gabrielsen TO, Aisen AM (1986) Patients with partial seizures: evaluation by MR, CT, and PET imaging. *Radiology,* **159**, 159–163.

Lesser RP, Modic MP, Weinstein MA, Duchesneau PM, Lüders H, Dinner DS *et al.* (1986) Magnetic resonance imaging (1.5 tesla) in patients with intractable focal seizures. *Archives of Neurology, Chicago,* **43**, 367–371.

McLachlan RS, Black S, Nicholson RL, Blume WT (1984) Nuclear magnetic resonance, a new approach to imaging in temporal lobe epilepsy. *Epilepsia,* **25**, 650.

McLachlan RS, Nicholson RL, Black S, Carr T, Blume WT (1985) Nuclear magnetic resonance imaging, a new approach to the investigation of refractory temporal lobe epilepsy. *Epilepsia,* **26**, 555–562.

Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE (1979) Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: validation of method. *Annals of Neurology,* **6**, 371–388.

Radtke RA, McNamara JO, Lewis DV, Heinz ER (1986) Usefulness of magnetic resonance imaging in presurgical evaluation of intractable complex partial seizures. *Epilepsia,* **27**, 612.

Radtke RA, Hoffman JM, Hanson MW, Walczak TS, Lewis DV, Coleman RE (1990) Temporal PET hypometabolism: predictor of positive outcome after temporal lobectomy. *Epilepsia,* **31**, 626.

Riela AV, Penry JK, Laster DW, Schartze M (1984) Magnetic resonance imaging versus computerized cranial tomography in complex partial seizures. *Epilepsia,* **25**, 650.

Rougier A, Biset JM, Kien P, Loiseau P, Caille JM (1988) I.R.M. et chirurgie de l'épilepsie. *Neurochirurgie,* **34**, 188–193.

Rowe CC, Berkovic SF, Sia STB, Austin M, McKay WJ, Kalnins RM *et al.* (1989) Localization of epileptic foci with postictal single photon emission computed tomography. *Annals of Neurology,* **26**, 660–668.

Ryvlin P, Garcia-Larrea L, Philippon B, Froment JC, Fischer C, Revol M, Mauguière F (1991) High signal intensity on T2-weighted MRI correlates with hypoperfusion in temporal lobe epilepsy. *Epilepsia.* In press.

Sackellares JC, Siegel GJ, Abou-Khalil BW, Hood TW, Gilman S, McKeever PE *et al.* (1990) Differences between lateral and mesial temporal metabolism interictally in epilepsy of mesial temporal origin. *Neurology, Cleveland,* **40**, 1420–1426.

Schorner W, Meencke HJ, Felix R (1987) Temporal-lobe epilepsy: comparison of CT and MR imaging. *AJR: American Journal of Roentgenology,* **149**, 1231–1239.

Sokoloff L, Reivich M, Kennedy C, Des Rosiers MH, Patlak CS, Pettigrew KD *et al.* (1977) The [^{14}C]deoxyglucose method for the measurement of local cerebral glucose utilization: theory, procedure, and normal values in the conscious and anesthetized albino rat. *Journal of Neurochemistry,* **28**, 897–916.

Sperling MR, Wilson G, Engel J, Babb TL, Phelps M, Bradley W (1986) Magnetic resonance imaging in intractable partial epilepsy: correlative studies. *Annals of Neurology,* **20**, 57–62.

Sperling MR, Gur RC, Alavi A, Gur RE, Resnick S, O'Connor MJ *et al.* (1990) Subcortical metabolic alterations in partial epilepsy. *Epilepsia,* **31**, 145–155.

Stefan H, Pawlik G, Böcher-Schwarz HG, Biersack HJ, Burr W, Penin H *et al.* (1987) Functional and morphological abnormalities in temporal lobe epilepsy: a comparison of interictal and ictal EEG, CT, MRI, SPECT and PET. *Journal of Neurology,* **234**, 377–384.

Sussman NM, Scanlon M, Garfinkle W, Callanan M, Barry E, Katz RI *et al.* (1984) Magnetic resonance imaging in temporal lobe epilepsy: comparison with EEG and computerized tomography. *Epilepsia*, **25**, 649–650.

Theodore WH, Newmark ME, Sato S, Brooks R, Patronas N, De La Paz R *et al.* (1983) [^{18}F]fluorodeoxyglucose positron emission tomography in refractory complex partial seizures. *Annals of Neurology*, **14**, 429–437.

Theodore WH, Dorwart R, Holmes M, Porter RJ, DiChiro G (1986) Neuroimaging in refractory partial seizures: comparison of PET, CT, and MRI. *Neurology, Cleveland*, **36**, 750–759.

Theodore WH, Fishbein D, Dubinsky R (1988) Patterns of cerebral glucose metabolism in patients with partial seizures. *Neurology, Cleveland*, **38**, 1201–1206.

Theodore WH, Katz D, Kufta C, Sato S, Patronas N, Smothers P *et al.* (1990) Pathology of temporal lobe foci: correlation with CT, MRI, and PET. *Neurology, Cleveland*, **40**, 797–803.

Triulzi F, Franceschi M, Fazio F, Del Maschio A (1988) Nonrefractory temporal lobe epilepsy: 1.5-T MR imaging. *Radiology*, **166**, 181–185.

Valk PE, Laxer KD, Knezevic S, Jagust WJ, Dillon WP, Barbaro NM (1990) High-resolution PET and MRI of mesial temporal sclerosis in partial complex epilepsy. *Journal of Nuclear Medicine*, **31**, 880.

Yamamoto YL, Ochs R, Gloor P, Ammann W, Meyer E, Evans AC *et al.* (1983) Patterns of rCBF and focal energy metabolic changes in relation to electroencephalographic abnormality in the interictal phase of partial epilepsy. In: *Cerebral Blood Flow, Metabolism and Epilepsy.* Edited by M. Baldy-Moulinier, D. H. Ingvar, and B. S. Meldrum London: John Libbey, pp. 51–62

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'SO-CALLED' CORTICAL DEAFNESS

CLINICAL, NEUROPHYSIOLOGICAL AND RADIOLOGICAL OBSERVATIONS

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SUMMARY

Two patients with severe, persistent hearing loss caused by bilateral cerebral lesions are described. To determine the location of lesions responsible for the severe hearing loss, we examined magnetic resonance images and compared the lesions in these 2 patients with those in another with only mild hearing loss following extensive bilateral temporoparietal lesions. The extent of bilateral damage to the white matter adjacent to the posterior half of the putamen proved crucial in determining the severity of the hearing loss. Hearing loss was more severe when the white matter immediately ventral and lateral to the posterior half of the putamen was involved bilaterally. Based on this observation and from a review of the literature, we infer that the auditory radiations in humans course in a dense tract from the medial geniculate body up to the sublenticular region, and disperse from there to the primary auditory cortex as well as to the other auditory-related areas, partly by coursing through the white matter immediately ventral to the posterior half of the putamen, and partly by penetrating the ventral and lateral portions of the posterior half of the putamen. Accordingly, bilateral lesions in the white matter ventral and lateral to the posterior half of the putamen appear to interrupt all the projection fibres from the medial geniculate bodies to the auditory-related areas, resulting in severe, persistent hearing loss.

INTRODUCTION

Severe auditory deficit due to bilateral cerebral lesions is relatively rare. This condition is generally called 'cortical deafness', since most cases have damage to the bilateral temporal or temporoparietal lobes, including the primary auditory cortex (areas 41 and 42) on both transverse gyri (Heschl). However, results of recent studies on humans and animals have led authors to question whether bilateral lesions in the primary auditory cortex cause severe, persistent hearing loss. As Vignolo (1969) pointed out, cases have been reported in which only minimal hearing loss was detected by audiometry, despite bilateral temporal lobe lesions destroying or disconnecting Heschl's gyri. Experimental evidence also exists which supports the idea that bilateral ablation of the primary auditory cortex in animals does not cause permanent deafness, although a transient decrease in acuity may be observed (Neff *et al.*, 1975).

Recently, we have had an opportunity to examine 2 patients with severe, persistent hearing loss caused by purely cerebral pathology. Using magnetic resonance imaging

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(MRI), we compared the lesions in these patients with those in a patient we had previously reported who showed only mild hearing loss despite extensive bilateral temporoparietal lesions. In the light of our own findings and from a review of the literature, we discuss the cerebral lesions that would cause severe, persistent hearing loss and other 'cortical' auditory disorders in man.

CASE REPORTS

Patient 1

A 48-yr-old, right-handed businessman with a history of hypertension for 20 yrs was admitted to Jichi Medical School Hospital on October 11, 1988, for evaluation of his hearing disorder.

On July 27, 1981, at age 41 yrs, he experienced a sudden onset of drooling from the left corner of his mouth and left hemiparesis. He was brought to a local hospital, where he was unconscious for several days. Computed tomography (CT) of the brain revealed a haemorrhage in the right putamen, which was aspirated 3 days after the onset of the symptoms. Three months later he was discharged with a mild weakness in his left upper extremity and returned to his previous work without any hearing disturbance.

On June 18, 1988, the patient suddenly became dazed and mute with right hemiparesis. He was admitted to another hospital where CT of the brain showed a new haematoma in the left putamen, which was removed 7 days after the onset of the symptoms. The disturbed consciousness and right hemiparesis resolved gradually. One month later he noticed a severe hearing disturbance.

On admission he did not respond to verbal questions or environmental sounds and did not startle to loud noises. He was attentive and cooperative, and was orientated to time and place with a good insight into his illness. His blood pressure was 150/110 mmHg and his heart rate 75/min with normal sinus rhythm. Tests of remote as well as recent memory, constructions and calculations were normal. General neurological examination demonstrated a mild dysarthria and right hemiparesis; deep tendon reflexes were slightly increased bilaterally with a right-side accentuation. No pathological reflexes were elicited. The gait showed a slight circumduction of the right leg. Sensory and cerebellar tests were unremarkable.

Neuropsychological examination revealed abnormally loud spontaneous speech without paraphasic errors. Visual confrontation naming, reading aloud and comprehension, and spontaneous writing were normal. The Token Test presented by written commands on October 25, 1988, was 97% correct. The patient showed no ideomotor or buccofacial apraxias to written commands. EEG showed mildly persistent slow waves in the right parietal region.

Patient 2

The patient is a 38-yr-old, right-handed electrical engineer.

On July 23, 1979, at age 30 yrs, the patient suddenly became dazed and dysarthric. He was brought to a local hospital immediately, where CT of the brain revealed a low-density in the right temporoparietal area. A right carotid angiogram demonstrated occlusion of the internal carotid artery near the bifurcation. Three days after admission he had a generalized convulsion. The patient was discharged on phenytoin and phenobarbital 3 wks later, and returned to work uneventfully.

On October 3, 1986, the patient again abruptly became dazed and unable to speak. He was admitted to the same hospital, where he was mute and gave no response to verbal commands. CT of the brain revealed a new ischaemic lesion in the left temporoparietal region. A left carotid angiogram demonstrated obstruction in the proximity of the trifurcation of the middle cerebral artery with retrograde filling from other vessels. He gradually regained the ability to speak a word or two. Although a moderate number of verbal and literal paraphasias contaminated his spontaneous speech initially, they gradually decreased with time, and he became able to follow simple written commands. However, he gave no response to verbal commands, nor did he startle to loud noises. The admitting physician had an impression of 'cortical deafness' and referred him to Jichi Medical School Hospital on February 2, 1987, for further evaluation.

On admission the patient was alert, and general physical examination revealed a normal heart rate and rhythm with a blood pressure of 120/70 mmHg. No carotid bruits were audible. General neurological examination was normal except for a moderate dysarthria and deafness. The patient himself stated that he was deaf.

Neuropsychological examination showed occasional verbal and literal paraphasias in spontaneous speech and in naming common objects presented visually. He was able to understand and execute simple written commands but not complex ones. The Token Test presented by written commands on March 20, 1987, was 70% correct. Both spontaneous writing and copying of letters and sentences showed some spelling errors. Graphic constructional ability was mildly impaired. No ideomotor or buccofacial apraxias to written commands were observed. EEG showed mild to moderate persistent slow waves in the bilateral parietal regions, with some accentuation on the right.

The patient appeared totally deaf with no signs of discomfort to loud speech, and at no stage could he understand speech. However, his parents reported that he seemed to perceive some noises, because he would turn his head to the sirening of an ambulance or ringing of a telephone occasionally.

INVESTIGATIONS AND RESULTS

Neuroanatomical investigation

A Toshiba MRI scanner (1.5 tesla) was used to obtain 5 mm thick axial and coronal T1-weighted inversion recovery images, using a repetition time of 2.5 s, an echo time of 30 ms, and an inversion time of 600 ms. To compare the extent of the lesions, the line connecting the anterior and posterior commissures was adopted as a reference axis for axial sections, and the line perpendicular to it at the anterior commissure as a reference axis for coronal sections. The computer was programmed to place the position of the anterior commissure just below the junction of the anterior corpus callosum and fornix. The posterior commissure was marked at the most superior point of the midbrain aqueduct.

Patient 1. Both axial and coronal sections showed irregular haematoma cavities bilaterally in the deep white matter underlying the insular cortex, especially of its posterior half, with varying degrees of destruction of the putamen. The right side was more extensively involved than the left (Fig. 1A,B). On coronal sections the lesions extended to the ventral and lateral parts of the posterior half of the putamen and the adjacent white matter bilaterally (Fig. 1B). Heschl's gyri were spared completely on both sides; the white matter underlying Heschl's gyrus was spared completely on the left side, but was involved partially on the right in either view.

Patient 2. The lesion was more extensive on the right in both views, where all of Heschl's gyrus and its underlying white matter, the insular cortex and its underlying white matter, the external capsule, the outer portion of the putamen, the inferior frontal lobe, and the parietal lobe were damaged; the smaller left-sided lesion involved the posterior half of the insular cortex and its underlying white matter, a portion of the external capsule, part of Heschl's gyrus and its underlying white matter, and the parietal lobe (Fig. 2A,B).

Audiological examination

Both patients had normal external auditory meatus and eardrums, and had normal tympanograms bilaterally. Acoustic reflexes, ipsilateral and contralateral, were elicited at normal thresholds. Standard pure-tone threshold audiometry on admission showed a severe sensorineural hearing loss in both patients, more severe in patient 1, with greater variability in the responses in both ears (Figs 3, 4). Of 24 different environmental sounds presented using a tape recorder, including sound-producing objects, animals or events, patient 1 identified none and patient 2 identified only 2: ambulance siren and telephone

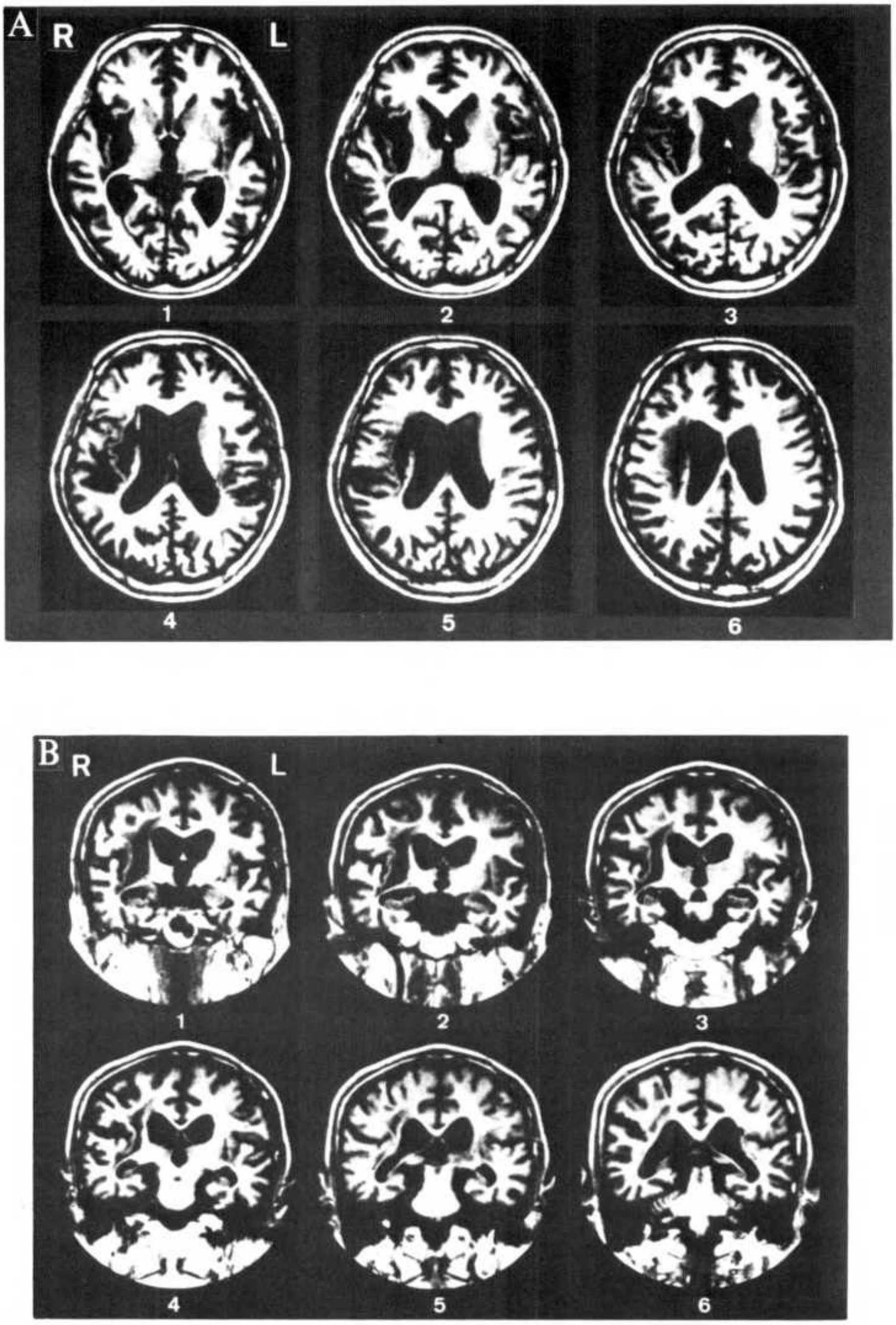

FIG. 1. MRIs of patient 1 showing bilateral irregular haematoma cavities in the deep white matter underlying the insular cortex, especially of its posterior half, with varying degrees of destruction of the putamen. Heschl's gyri are spared completely on both sides; the white matter underlying Heschl's gyrus is spared completely on the left, but is involved partially on the right. A, B show axial and coronal sections, respectively.

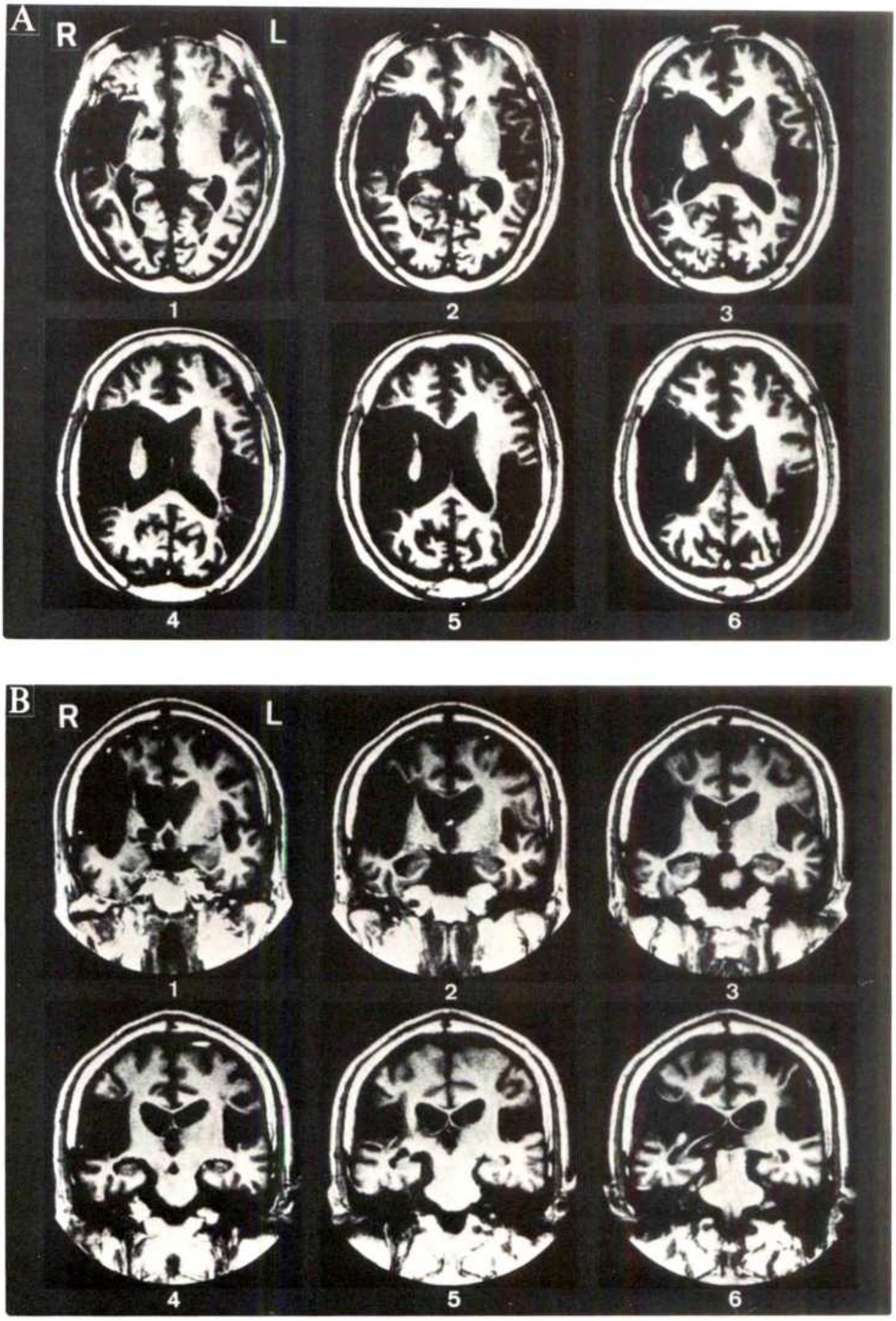

FIG. 2. MRIs of patient 2 showing bilateral temporoparietal lesions involving the deep white matter underlying the insular cortex, especially of its posterior half. Heschl's gyrus and its underlying white matter on the right are involved completely; on the left, Heschl's gyrus and its immediately underlying white matter are damaged in part. A, B show axial and coronal sections, respectively.

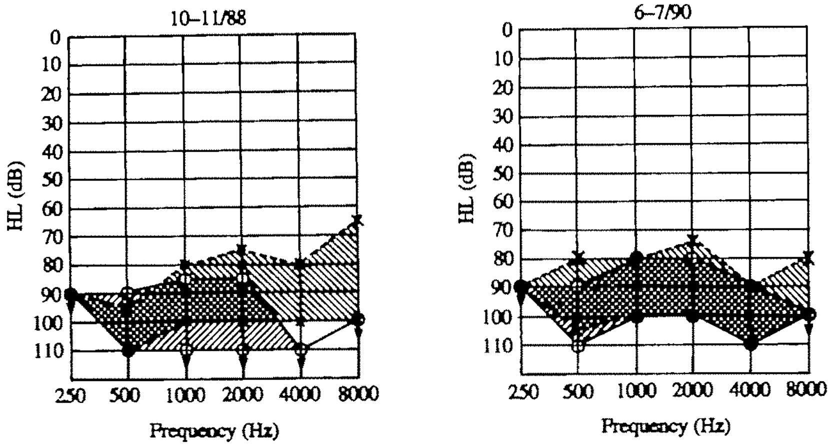

FIG. 3. Pure-tone threshold audiometry was performed on 4 occasions in patient 1 during his initial hospitalization (*left*). A severe sensorineural hearing loss in both ears with great variability was detected. Audiogram re-examined on 3 occasions 20 mths later (*right*) is relatively unchanged, although it shows less variability x = left ear; o = right ear; HL = hearing level. Arrows indicate values scaled out. Shading at 45° (right ear) and 135° (left ear) shows a variable and fluctuating hearing range.

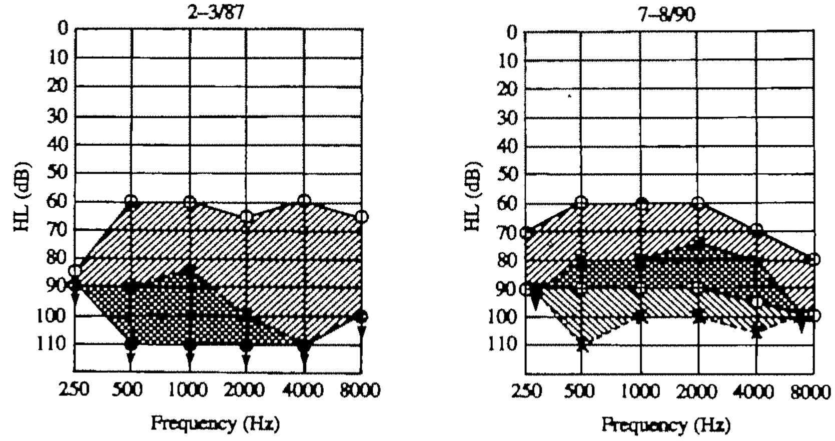

FIG. 4 Pure-tone threshold audiometry was performed on 4 occasions in patient 2 during the initial hospitalization (*left*). A severe sensorineural hearing loss with great variability was detected in both ears, which was more profound on the left. Audiogram re-examined on 3 occasions 41 mths later (*right*) is almost unchanged, although it shows less variability. x = left ear; o = right ear; HL = hearing level Arrows indicate values scaled out. Shading at 45° (right ear) and 135° (left ear) shows a variable and fluctuating hearing range.

ringing. In an identification test of 100 randomly-ordered vowels (a, e, i, o, u) presented by a native male Japanese voice, the average correct response across all the 5 vowels was 18% in patient 1 and 32% in patient 2, the former being at a chance level and the latter slightly better than that. Audiograms of patients 1 and 2 re-examined 20 and 41 mths later, respectively, were almost unchanged (Figs 3, 4). At that time, patient 1 and his wife reported no improvements in hearing, except for occasional reactions to some loud sounds such as a doorbell or klaxon. He could rarely recognize some loud sounds such as crashing peals of thunder. Patient 2 and his parents also reported no improvements, except that at times he recognized some loud sounds such as howling of a storm or slamming of a door. Both patients also complained that some slightly loud sounds often buzzed or roared disagreeably in their ears.

Auditory evoked potentials

Patient 1 was examined on October 17, 1988, and patient 2 on February 19, 1987. Stimuli were presented at 90 dB HL monaurally via shielded headphones. The contralateral ear was masked for all trials. Brainstem auditory evoked potentials (BAEPs) were recorded by averaging 2048 repetitions of 10 ms epochs elicited by 0.1 ms rarefaction clicks at a rate of 10 Hz, using bandpass from 100 to 3000 Hz. Middle latency auditory evoked potentials (MLAEPs) were recorded by averaging 1024 repetitions of 50 ms epochs elicited by 0.1 ms rarefaction clicks at a rate of 5 Hz, using bandpass from 5 to 1000 Hz. Late latency auditory evoked potentials (LLAEPs) were recorded by averaging 128 repetitions of 500 ms epochs elicited by 1000 Hz tone bursts of 50 ms with 7 ms rise and fall times at a rate of 0.5 Hz randomly, using bandpass from 0.5 to 30 Hz. Recordings of BAEPs were derived from the vertex (Cz), and those of MLAEPs and LLAEPs from C3, C4 and Cz, all referenced to the earlobe (A1 or A2) of the stimulated side.

All BAEP components (waves I–VI) were recorded with normal latency in both patients, but the main component (Pa) of the MLAEPs was not recorded reliably from either hemisphere under any condition in either patient (Figs 5, 6). As for LLAEPs, the N1 and P2 were obtained in patient 1, and the N1, P2 and N2 were obtained in patient 2, although low in amplitude in both cases (Figs 5, 6). However, the latency of each component could not be determined, because the responses were somewhat variable and inconsistent in both patients, especially in patient 1.

DISCUSSION

The normal tympanograms, acoustic reflexes and brainstem auditory evoked responses in the present 2 patients indicated that the functional integrity of the auditory pathways from the middle ear to the inferior colliculi was intact bilaterally.

Patient 1 had been almost totally deaf for 2 yrs following the second of 2 haemorrhages which destroyed the white matter immediately ventral and lateral to the posterior half of the putamen on both sides with variable degrees of destruction of the nuclei. Patient 2 had a slightly less severe hearing loss for about 4 yrs following the second of 2 cerebral infarctions which involved the posterior half of the insular cortex and its underlying deep white matter, and the parietal lobe bilaterally; Heschl's gyrus and its underlying white matter had been destroyed completely on the right and partially on the left. Thus both patients had bilateral damage to the deep white matter underlying the posterior half of the insular cortex in common.

A number of patients have been reported who had severe hearing loss after bilateral temporal or temporoparietal lesions (Jerger *et al.*, 1969; Lhermitte *et al.*, 1971; Adams *et al.*, 1977; Earnest *et al.*, 1977; Kobayashi *et al.*, 1977; Graham *et al.*, 1980;

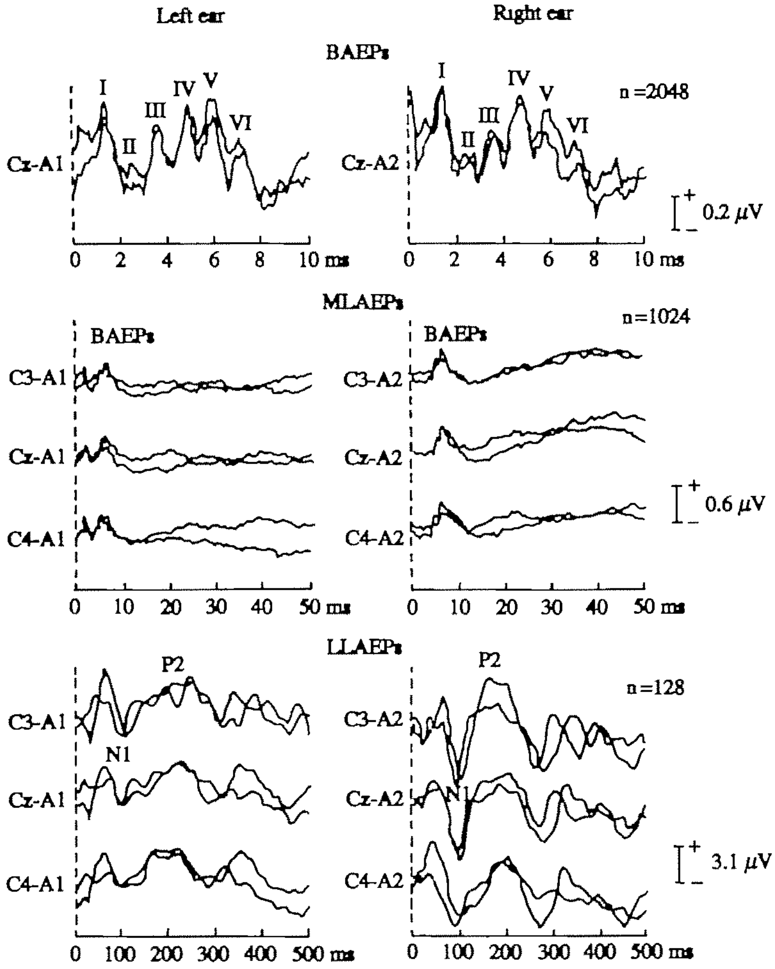

FIG 5 Brainstem auditory evoked potentials (BAEPs; *top*), middle latency auditory evoked potentials (MLAEPs; *middle*), and late latency auditory evoked potentials (LLAEPs; *bottom*) in patient 1. Waves I–VI in the BAEPs are intact in both tracings. Note complete absence of the Pa component of the MLAEPs, which should occur at about 30 ms after the auditory stimuli. The N1 and P2 components of the LLAEPs are elicited, although somewhat variable in both amplitude and latency.

Leicester, 1980; Özdamar *et al.*, 1982; Woods *et al.*, 1984; Bahls *et al.*, 1988; Mendez and Geehan, 1988) or bilateral subcortical lesions (Hirano, 1973, 1983; Kitahara *et al.*, 1979; Ueda *et al.*, 1981; Nishikawa *et al.*, 1983; Nakayama *et al.*, 1986; Hasegawa *et al.*, 1989). However, in most of the cases, the severe hearing loss eventually resolved with only minor residual audiometric deficit accompanied by varying degrees of impairment in the ability to interpret non-verbal as well as verbal sounds (word deafness or auditory agnosia). Only 6 patients actually suffered from severe hearing loss which persisted for more than 6 mths: 4 after infarctions in the bilateral temporal or temporoparietal lobes (Earnest *et al.*, 1977; Graham *et al.*, 1980; Özdamar *et al.*, 1982;

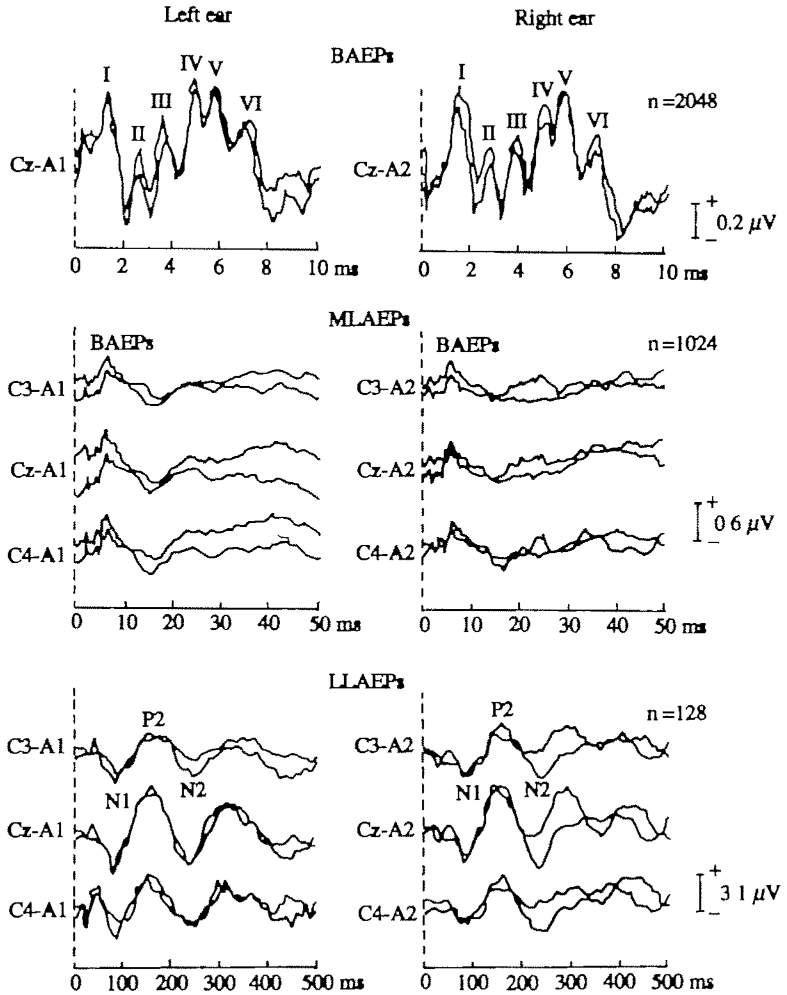

FIG. 6. Brainstem auditory evoked potentials (BAEPs, *top*), middle latency auditory evoked potentials (MLAEPs; *middle*), and late latency auditory evoked potentials (LLAEPs; *bottom*) in patient 2. As in patient 1, waves I–VI in the BAEPs are intact. The Pa component of the MLAEPs, however, is absent completely. The N1, P2 and N2 components of the LLAEPs are elicited

Bahls *et al.*, 1988); and 2 after haemorrhages in the bilateral putamens (Hirano, 1973, 1983; Nakayama *et al.*, 1986). Hirano's case (1973, 1983) is particularly interesting in that it provides an important clue to the understanding of the neuroanatomical basis for severe hearing loss of cerebral origin. His patient remained completely deaf until death 4 yrs after the second of 2 bilateral haemorrhages in the putamen. Autopsy revealed symmetrical slit-shaped haematoma cavities in the deep white matter underlying the bilateral insular cortices and Heschl's gyri. Microscopically the auditory radiations and the medial geniculate bodies (MGBs) had been degenerated completely on both sides. Before the advent of modern audiology, Clark and Russell (1938) described a deaf patient with lesions similar to those in Hirano's case, although the lesions were less extensive and limited to the external capsules with variable degrees of bilateral destruction of the ventrolateral portion of the putamen and its adjacent white matter. This patient also had complete degeneration of the auditory radiations and the MGBs bilaterally. Thus the severe hearing loss in our 2 patients appears to be the result of bilateral destruction of the auditory radiation underlying the insular cortex.

The auditory radiation is generally believed to emerge from the MGB and project mainly to Heschl's gyrus by passing through the sublenticular portion of the internal capsule (Carpenter and Sutin, 1983). Accordingly, bilateral lesions limited to Heschl's gyrus and/or its subjacent auditory radiation should result in severe, persistent hearing loss. However, as already noted, there are reports that the complete bilateral destruction of those structures produced only minimal hearing loss (Wohlfart *et al.*, 1952; Mahoudeau *et al.*, 1958). We must therefore explain why bilateral damage to the auditory radiation underlying the insular cortex causes severe, persistent hearing loss, as in our patients.

A review of autopsy studies on 'cortical' auditory disorders reveals that patients with minimal audiometric hearing loss had minimal change on one or both MGBs (Wohlfart *et al.*, 1952; Lhermitte *et al.*, 1971; Oppenheimer and Newcombe, 1978; Leicester, 1980), and that patients with severe, persistent hearing loss had severe retrograde degeneration throughout the MGBs bilaterally, whether the deafness was cortical (Bahls *et al.*, 1988) or subcortical (Clark and Russell, 1938; Hirano, 1973, 1983). This suggests that, in humans, cortical and/or subcortical lesions extensive enough to denervate all or almost all of the MGBs on both sides will cause marked, persistent hearing loss. Landau *et al.* (1960) described a child who showed nearly normal audiometry despite severe degeneration of both MGBs, probably caused by destruction of the bilateral perisylvian structures on both sides in infancy. A degree of compensation may differ between infants and adults after equivalent lesions. Scharlock *et al.* (1963) indicated that, in cats, damage to the entire auditory cortex with medial geniculate connections during infancy causes less impairment in the ability to learn a pattern and a duration discrimination than the same lesion sustained at maturity. Also, Heffner and Heffner (1986) demonstrated that, in monkeys, only mild hearing loss of about 20–40 dB on the average persisted in the mid-frequency range on audiometry after bilateral ablation of almost all the cortex with medial geniculate connections, although hearing loss was severe initially. Animals may have somewhat less severe, lasting audiometric loss than humans, even if comparable lesions were made at maturity. A difference in the effect of lesions between humans and monkeys is also described in the visual capacity after damage to visual cortex (Weiskrantz *et al.*, 1974).

There are direct medial geniculate projections to cortical areas outside of the primary auditory cortex in animals and humans. In rhesus monkeys, for example, the anterior parvocellular medial geniculate nucleus projects largely to the primary auditory cortex, and the posterior parvocellular medial geniculate nucleus projects mainly to the auditory association cortex; the suprageniculate subdivision of the medial geniculate complex may send projections to the frontoparietal operculum and the insula (Mesulam and Pandya, 1973). Also in humans, Heschl's gyrus has been shown to receive essential projections from the parvocellular portion and a part of the magnocellular division of the nucleus; the supramarginal gyrus and caudal insula apparently receive projections from the magnocellular portion (Locke *et al.*, 1962). Furthermore, in humans, there is electrophysiological evidence that some cortical areas outside of Heschl's gyrus also may have auditory function. Celesia (1976) studied open-brain recording of auditory evoked potentials elicited by click stimulation during neurosurgical procedures and found a large auditory-related area surrounding the primary auditory cortex which extends to the posterior two-thirds of the superior temporal gyrus and the upper bank of the sylvian fissure, including the frontal and parietal operculi. In 1 patient, the responses recorded from the superior bank of the sylvian fissure persisted after resection of the ipsilateral primary auditory cortex. This is in good agreement with the cytoarchitectural study of Galaburda and Sanides (1980) who found auditory-related cortex in the inferior parietal lobule as well. It is likely, therefore, that, in humans, extensive degeneration of the MGBs will be caused by bilateral destruction of all the auditory-related areas that include Heschl's gyrus, the posterior two-thirds of the superior temporal gyrus, the superior bank of the sylvian fissure and the inferior parietal lobule, or of all the projection fibres thereto.

We previously reported a patient with word deafness who had only mild audiometric deficit despite extensive temporoparietal lesions bilaterally (Tanaka *et al.*, 1987). We repeated MRI on this patient using the same reference axes as in patients 1 and 2, and found that only a small part of the white matter underlying Heschl's gyrus was spared on each side (Fig. 7A,B). The relatively well-preserved hearing in this patient might have been due to this spared area. However, another explanation is possible, since there are reports of patients who showed only slight hearing loss despite complete destruction of Heschl's gyri and/or its underlying white matter bilaterally (Wohlfart *et al.*, 1952; Mahoudeau *et al.*, 1958). By comparing the lesions in this word-deaf patient with those in the present 2 patients, we found that the extent of bilateral damage to the white matter adjacent to the posterior half of the putamen was crucial in determining the severity of the hearing loss. In patient 1 with the most severe hearing loss, all the white matter immediately ventral and lateral to the posterior half of the putamen was involved bilaterally. In patient 2 with slightly less severe hearing loss, all or almost all the white matter lateral to the posterior half of the putamen was involved bilaterally, although the white matter ventral to the posterior half of the putamen, especially on the left, was less involved than in patient 1 (Fig. 8). The word-deaf patient with only minor hearing loss, on the other hand, had little or no damage to the white matter ventral to the posterior half of the putamen on either side; the upper one-third to one-half of the lateral portion of the posterior half of the putamen and its adjacent white matter was spared on the right side and the upper one-fifth to one-fourth of the same region was spared on the left side. Furthermore, in this patient, the superior bank of the sylvian fissure was almost spared on the right and partially on the left (Fig. 8). Based on these findings and the above-cited literature, we infer that, in humans at least, the auditory radiations travel densely from the MGB up to the sublenticular region, and disperse from there to Heschl's gyrus as well as to the other auditory-related areas, such as the posterior two-thirds of the superior temporal gyrus, the upper bank of the sylvian fissure including the frontoparietal operculum and the inferior parietal lobule, partly by coursing through the white matter immediately ventral to the posterior half of the putamen, and partly by penetrating the ventral and lateral portions of the posterior half of the putamen, although the major projections are to Heschl's gyrus. This hypothesis is supported partially by the experimental work in monkeys done by Poliak (1932) who showed that the auditory

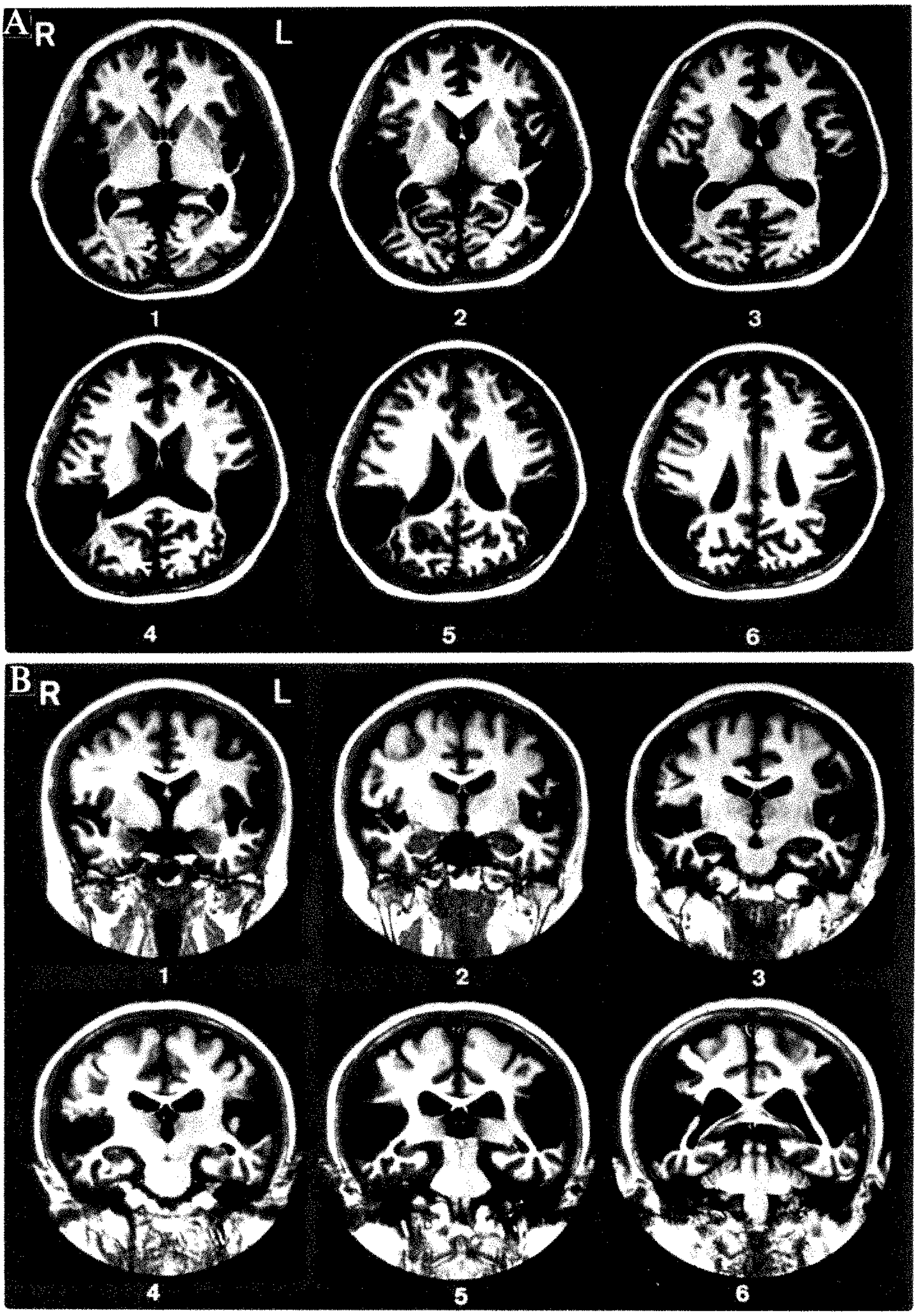

FIG. 7. MRIs of a word-deaf patient with only mild hearing loss (average, 15 dB right ear and 8 dB left ear, from 500 to 2000 Hz 4 mths after the onset of the symptom). A Picker Vista MRI scanner operating at 1.5 tesla was used to obtain 5 mm thick axial and coronal T_1-weighted inversion recovery images. Reference axes for axial and coronal sections are the same as those used in patients 1 and 2. Note extensive bilateral temporoparietal lesions, greater on the right. Only a small part of the white matter underlying Heschl's gyrus is spared on each side. A, B show axial and coronal sections, respectively.

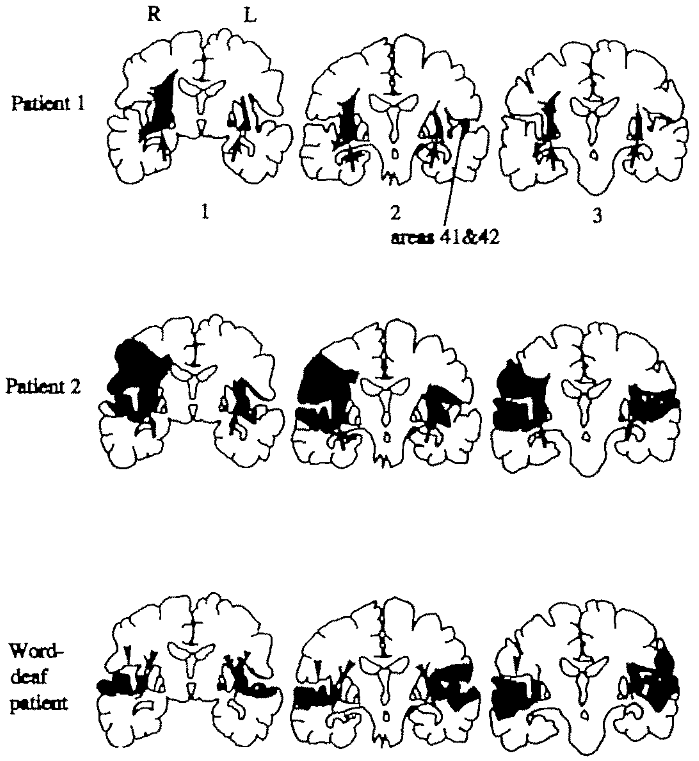

FIG. 8 Schematic coronal views of the lesions in patient 1 (*upper*), patient 2 (*middle*) and the word-deaf patient with only mild hearing loss (*bottom*) Areas of destruction are shown in black. Areas 41 and 42 are the primary auditory area. Note that patient 1, with the most severe hearing loss, has lesions much deeper to the insular cortex, which extend to the ventral portion of the posterior half of the putamen and its immediately adjacent ventral white matter bilaterally (large arrows) Patient 2, with less severe hearing loss, has less extensive lesions bilaterally (small arrows) than patient 1, but more extensive than the word-deaf patient with mild hearing loss. Also, both patients 1 and 2 have lesions extending into all or almost all the white matter lateral to the posterior half of the putamen bilaterally. In the word-deaf patient, on the other hand, the upper one-third to one-half of the lateral portion of the posterior half of the putamen and its adjacent white matter as well as the superior bank of the sylvian fissure are spared on the right (large arrowheads), the upper one-fifth to one-fourth of the lateral portion of the posterior half of the putamen and its adjacent white matter and a part of the superior bank of the sylvian fissure are spared on the left (small arrowheads).

radiations reach the cortex partly by coursing immediately ventral to the lentiform nucleus and partly by penetrating its ventral portion. Accordingly, bilateral lesions in the white matter ventral and lateral to the posterior half of the putamen appear to interrupt all the projection fibres from the MGBs to the auditory-related cortices, resulting in severe, persistent hearing disturbance. Even if all of Heschl's gyrus and its immediately underlying auditory radiation are destroyed bilaterally, hearing will recover if the other auditory-related areas and the projection fibres to these areas are spared on one or both sides.

In recent years, word deafness caused by bilateral infarctions of the primary auditory cortex (Coslett *et al.*, 1984) or by bilateral damage to its underlying deep white matter (Brick *et al.*, 1985) has been reported. A word-deaf patient with lesions similar to those described by Coslett *et al.* (1984) has been reported earlier by Kanshepolsky *et al.* (1973).

Furthermore, Goldstein (1927), in his discussion of the localization of word deafness caused by bilateral lesions, placed the responsible lesion in the middle portion of the superior temporal gyrus. These suggest that comprehension of verbal sounds may be mediated mainly by the pathway into and from Heschl's gyrus. The pathology of auditory agnosia for environmental sounds, on the other hand, has been variable. It has been reported to be caused by unilateral lesions of the right hemisphere which involved the upper bank of the sylvian fissure and the inferior parietal lobule most severely (Spreen *et al.*, 1965), or by probably bilateral temporoparietal lesions (Albert *et al.*, 1972), or by unilateral lesions of the left hemisphere (Spinnler and Vignolo, 1966; Faglioni *et al.*, 1969; Albert *et al.*, 1971). Motomura *et al.* (1986) recently reported an interesting case of auditory agnosia caused by bilateral subcortical lesions adjoining the MGB. Their case is unique in that the clinical picture began with generalized auditory agnosia for both verbal and environmental sounds, which changed, over 2 mths, to selective auditory agnosia for environmental sounds. This indicates that the auditory processing mechanisms for verbal and environmental sounds may be different, even at a subcortical level. Furthermore, a review of the extent of the lesions determined by autopsy or MRI in the reported cases of generalized auditory agnosia shows that, in addition to bilateral lesions in Heschl's gyrus and/or its underlying deep white matter, these cases had lesions involving most of the white matter lateral to the putamen, especially of its posterior half, either on the left (Mahoudeau *et al.*, 1958; Oppenheimer and Newcombe, 1978) or the right (Wohlfart *et al.*, 1952; Leicester, 1980; Kazui *et al.*, 1990), or had extensive damage to the ventral portion of the posterior part of the putamen and/or its adjacent ventral white matter on the left side or partial damage to these areas on both sides (Lhermitte *et al.*, 1971; Hasegawa *et al.*, 1989). Although Lhermitte *et al.* (1971) did not represent these lesions in their schemata, the photographs of the actual specimens seem to have lesions partly extending into the white matter ventral to the posterior part of the putamen on both sides. From these considerations and our experience in the word-deaf patient with relatively well-preserved ability to recognize environmental sounds, we speculate that comprehension of environmental sounds may be mediated mainly by the pathways from the MGB up to the upper bank of the sylvian fissure including the frontoparietal operculum and to the inferior parietal lobule, by penetrating the ventral portion of the posterior half of the putamen and the upper one-third to one-half of the lateral portion of the posterior half of the putamen on either side, although some mediation to the posterior two-thirds of the superior temporal gyrus by coursing through the deep white matter underlying Heschl's gyrus may also exist. Indeed, these hypothesized tracts seem to be relatively well preserved bilaterally in the autopsy case of word deafness that developed after bilateral cerebral haemorrhages involving the putamen (Brick *et al.*, 1985). Thus, in studying 'cortical' auditory disorders, it is necessary to consider subcortical as well as cortical lesions.

Our patients exhibited an intriguing auditory behaviour in naturalistic settings. They showed occasional unexpected reactions to environmental sounds despite concurrent absence of any reaction to loud noise. According to their families, they sometimes denied the sounds they reacted to. This phenomenon is similar to 'blindsight' seen in cortical blindness, which is characterized by tacit awareness of stimuli that cannot be consciously recollected (Weiskrantz *et al.*, 1974). However, their families also reported that the patients could certainly recognize some environmental sounds, although rarely in patient 1 and occasionally in patient 2. From these observations, the great variability on audiograms in our patients may be mainly caused by both selective disturbance of auditory attention and subliminal reception of sounds. Further investigation is necessary to clarify these physiological details.

Finally, in both of the present patients, the main component (Pa) of the MLAEPs was completely absent, while that (N1) of the LLAEPs was detected, although its amplitude was low. An opposite dissociation, preservation of the Pa in the absence of the N1, has been reported in lesion studies (Woods *et al.*, 1987; Bahls *et al.*, 1988). These suggest that the generator of N1 is independent of that of Pa. Although the location of the Pa generator is still controversial (Bahls *et al.*, 1988), the N1 generator has recently been localized to a site in the inferior parietal lobule (Woods *et al.*, 1987; Richer *et al.*, 1989). However, a discrepancy between auditory perception and evoked potential indices appears to exist. In the literature dealing with LLAEPs in 'cortical deafness', the response varies from a slightly elevated threshold (Earnest *et al.*, 1977) to complete absence (Hirano, 1973; Graham *et al.*, 1980; Bahls *et al.*, 1988). Similarly, MLAEPs in 'cortical deafness' vary from preservation (Bahls *et al.*, 1988) to complete absence (Graham *et al.*, 1980; Nakayama *et al.*, 1986). In addition, even in auditory agnosia or word deafness, LLAEPs and/or MLAEPs have been reported to be absent (Jerger *et al.*, 1969; Haguenauer *et al.*, 1979; Guard *et al.*, 1980; Michel *et al.*, 1980; Shindo *et al.*, 1981; Özdamar *et al.*, 1982; Lechevalier *et al.*, 1984; Marshall *et al.*, 1985; Motomura *et al.*, 1986; Mendez and Geehan, 1988; Hasegawa *et al.*, 1989). Thus, MLAEPs and LLAEPs do not seem to help discriminate 'cortical' auditory disorders specifically.

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REFERENCES

Adams AE, Rosenberger K, Winter H, Zöllner C (1977) A case of cortical deafness. *Archiv für Psychiatrie und Nervenkrankheiten*, **224**, 213–220.

Albert ML, Goldblum M-C, Benson DF, Hécaen H (1971) Mechanisms of auditory comprehension. II. Cerebral dominance *Transactions of the American Neurological Association*, **96**, 132–135.

Albert ML, Sparks R, von Stockert T, Sax D (1972) A case study of auditory agnosia: linguistic and non-linguistic processing. *Cortex*, **8**, 427–443.

Bahls FH, Chatrian GE, Mesher RA, Sumi SM, Ruff RL (1988) A case of persistent cortical deafness: clinical, neurophysiologic, and neuropathologic observations. *Neurology, Cleveland*, **38**, 1490–1493.

Brick JF, Frost JL, Schochet SS, Gutmann L, Crosby TW (1985) Pure word deafness: CT localization of the pathology. *Neurology, Cleveland*, **35**, 441–442.

Carpenter MB, Sutin J (1983) *Human Neuroanatomy*. Eighth edition. Baltimore and London: Williams and Wilkins, pp. 678.

Celesia GG (1976) Organization of auditory cortical areas in man. *Brain*, **99**, 403–414.

Clark WE Le G, Russell WR (1938) Cortical deafness without aphasia. *Brain*, **61**, 375–383.

Coslett HB, Brashear HR, Heilman KM (1984) Pure word deafness after bilateral primary auditory cortex infarcts. *Neurology, Cleveland*, **34**, 347–352.

EARNEST MP, MONROE PA, YARNELL PR (1977) Cortical deafness: demonstration of the pathologic anatomy by CT scan. *Neurology, Minneapolis*, **27**, 1172–1175.

FAGLIONI P, SPINNLER H, VIGNOLO LA (1969) Contrasting behavior of right and left hemisphere-damaged patients on a discriminative and a semantic task of auditory recognition. *Cortex*, **5**, 366–389.

GALABURDA A, SANIDES F (1980) Cytoarchitectonic organization of the human auditory cortex. *Journal of Comparative Neurology*, **190**, 597–610.

GOLDSTEIN K (1927) In: *Handbuch der Normalen und Pathologischen Physiologie*, Volume 10. Edited by A. Bethe, G. v. Bergmann, G. Embden and A. Ellinger. Berlin: Springer, p. 600. Cited by Geschwind N (1965) Disconnexion syndromes in animals and man. *Brain*, **88**, 237–294.

GRAHAM J, GREENWOOD R, LECKY B (1980) Cortical deafness: a case report and review of the literature. *Journal of Neurological Sciences*, **48**, 35–49.

GUARD O, COUAILLER JF, DUMAS R, ROMANET P, RICHARD D, MAUGUIERE F (1980) Agnosie auditive. *Lyon Médical*, **243**, 311–317.

HAGUENAUER J-P, SCHOTT B, MICHEL F, DEBREUIL C, ROMANET P (1979) Trois observations d'atteinte cortico-sous-corticale de l'audition: confrontations audiologique et tomodensimétriques. *Annales d'Oto-Laryngologie et de Chirurgie Cervico-Faciale*, **96**, 185–196.

HASEGAWA M, BANDO M, IWATA M, MANNEN T, KAGA K (1989) A case of auditory agnosia with the lesion of bilateral auditory radiation *Clinical Neurology, Tokyo*, **29**, 180–185 (in Japanese).

HEFFNER HE, HEFFNER RS (1986) Hearing loss in Japanese macaques following bilateral auditory cortex lesions. *Journal of Neurophysiology*, **55**, 256–271.

HIRANO M (1973) 'So-called' cortical deafness. *Psychiatria et Neurologia Japonica, Tokyo*, **75**, 94–138 (in Japanese).

HIRANO M (1983) What is 'Cortical Deafness'?: review of literature *Clinical Psychiatry, Tokyo*, **25**, 337–343 (in Japanese).

JERGER J, WEIKERS NJ, SHARBROUGH FW, JERGER S (1969) Bilateral lesions of the temporal lobe: a case study. *Acta Oto-Laryngologica*, Supplement 258, 1–51.

KANSHEPOLSKY J, KELLEY JJ, WAGGENER JD (1973) A cortical auditory disorder· clinical, audiologic and pathologic aspects. *Neurology, Minneapolis*, **23**, 699–705.

KAZUI S, NARITOMI H, SAWADA T, INOUE N, OKUDA J (1990) Subcortical auditory agnosia. *Brain and Language*, **38**, 476–487.

KITAHARA T, HAYAKAWA I, KANDA T, TAZAKI Y (1979) A case of subcortical deafness due to cerebral hemorrhage. *Japanese Journal of Stroke, Tokyo*, **1**, 360–364 (in Japanese).

KOBAYASHI I, SUGISHITA M, TOHGI H, KAGA K, KAMEYAMA M (1977) A case of cortical deafness. *Clinical Neurology, Tokyo*, **17**, 361–367 (in Japanese).

LANDAU WM, GOLDSTEIN R, KLEFFNER FR (1960) Congenital aphasia: a clinicopathologic study *Neurology, Minneapolis*, **10**, 915–921.

LECHEVALIER B, ROSSA Y, EUSTACHE F, SCHUPP C, BONER L, BAZIN C (1984) Un cas de surdité corticale épargnant en partie la musique. *Revue Neurologique*, **140**, 190–201.

LEICESTER J (1980) Central deafness and subcortical motor aphasia. *Brain and Language*, **10**, 224–242

LHERMITTE F, CHAIN F, ESCOUROLLE R, DUCARNE B, PILLON B, CHEDRU F (1971) Étude des troubles perceptifs auditifs dans les lésions temporales bilatérales (à propos de trois observations dont deux anatomo-cliniques). *Revue Neurologique*, **124**, 329–351.

LOCKE S, ANGEVINE JB, MARIN OSM (1962) Projection of the magnocellular medial geniculate nucleus in man. *Brain*, **85**, 319–330.

MAHOUDEAU D, LEMOYNE J, FONCIN J-F, DUBRISAY J (1958) Considérations sur l'agnosie auditive (à propos d'un cas anatomo-clinique). *Revue Neurologique*, **99**, 454–471.

MARSHALL RC, RAPPAPORT BZ, GARCIA-BUNUEL L (1985) Self-monitoring behavior in a case of severe auditory agnosia with aphasia. *Brain and Language*, **24**, 297–313.

MENDEZ MF, GEEHAN GR (1988) Cortical auditory disorders. clinical and psychoacoustic features. *Journal of Neurology, Neurosurgery, and Psychiatry*, **51**, 1–9.

MESULAM M-M, PANDYA DN (1973) The projections of the medial geniculate complex within the sylvian fissure of the rhesus monkey. *Brain Research, Amsterdam*, **60**, 315–333.

MICHEL F, PERONNET F, SCHOTT B (1980) A case of cortical deafness: clinical and electrophysiological data. *Brain and Language*, **10**, 367–377.

MOTOMURA N, YAMADORI A, MORI E, TAMARU F (1986) Auditory agnosia: analysis of a case with bilateral subcortical lesions. *Brain*, **109**, 379–391.

NAKAYAMA T, NOBUOKA H, WADA S, MATSUKADO Y (1986) Cortical deafness following bilateral hypertensive putaminal hemorrhage. *Brain and Nerve, Tokyo*, **38**, 565–570 (in Japanese).

NEFF WD, DIAMOND IT, CASSEDAY JH (1975) Behavioral studies of auditory discrimination: central nervous system. In: *Handbook of Sensory Physiology*, Volume 5, Part 2. Edited by W. D. Keidel and W. D. Neff. Berlin: Springer, pp. 307–400.

NISHIKAWA T, TABUSHI K, OKUDA J, TANABE H, SHIRAISHI J (1983) A case study of cortical deafness with reference to the active process in auditory perception. *Higher Brain Function Research, Tokyo*, **3**, 24–37 (in Japanese).

OPPENHEIMER DR, NEWCOMBE F (1978) Clinical and anatomic findings in a case of auditory agnosia. *Archives of Neurology, Chicago*, **35**, 712–719.

ÖZDAMAR Ö, KRAUS N, CURRY F (1982) Auditory brain stem and middle latency responses in a patient with cortical deafness. *Electroencephalography and Clinical Neurophysiology*, **53**, 224–230.

POLIAK S (1932) *The Main Afferent Fiber Systems of the Cerebral Cortex in Primates. University of California Publications in Anatomy*, Volume 2. Cited by Clark WE Le G, Russell WR (1938) Cortical deafness without aphasia. *Brain*, **61**, 375–383.

RICHER F, ALAIN C, ACHIM A, BOUVIER G, SAINT-HILAIRE J-M (1989) Intracerebral amplitude distributions of the auditory evoked potential *Electroencephalography and Clinical Neurophysiology*, **74**, 202–208.

SCHARLOCK DP, TUCKER TJ, STROMINGER NL (1963) Auditory discrimination by the cat after neonatal ablation of temporal cortex. *Science*, **141**, 1197–1198.

SHINDO M, KAGA K, TANAKA Y (1981) Auditory agnosia following bilateral temporal lobe lesions—report of a case. *Brain and Nerve, Tokyo*, **33**, 139–147 (in Japanese).

SPINNLER H, VIGNOLO LA (1966) Impaired recognition of meaningful sounds in aphasia *Cortex*, **2**, 337–348.

SPREEN O, BENTON AL, FINCHAM RW (1965) Auditory agnosia without aphasia. *Archives of Neurology, Chicago*, **13**, 84–92.

TANAKA Y, YAMADORI A, MORI E (1987) Pure word deafness following bilateral lesions: a psychophysical analysis. *Brain*, **110**, 381–403.

UEDA S, TSUDA T, MATSUMOTO K, OBAYASHI M, KOYAMA Y (1981) A moyamoya disease with cortical deafness. In: *Proceedings of the 10th Japanese Conference on Surgery of Cerebral Stroke*. Tokyo, pp. 105–109 (in Japanese).

VIGNOLO LA (1969) Auditory agnosia: a review and report of recent evidence. In: *Contributions to Clinical Neuropsychology*. Edited by A. L. Benton. Chicago: Aldine, pp. 172–231.

WEISKRANTZ L, WARRINGTON EK, SANDERS MD, MARSHALL J (1974) Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain*, **97**, 709–728.

WOHLFART G, LINDGREN Å, JERNELIUS B (1952) Clinical picture and morbid anatomy in a case of 'pure word deafness'. *Journal of Nervous and Mental Disease*, **116**, 818–827.

WOODS DL, KNIGHT RT, NEVILLE HJ (1984) Bitemporal lesions dissociate auditory evoked potentials and perception. *Electroencephalography and Clinical Neurophysiology*, **57**, 208–220.

WOODS DL, CLAYWORTH CC, KNIGHT RT, SIMPSON GV, NAESER MA (1987) Generators of middle- and long-latency auditory evoked potentials: implications from studies of patients with bitemporal lesions. *Electroencephalography and Clinical Neurophysiology*, **68**, 132–148.

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ROLE OF THE RIGHT TEMPORAL NEOCORTEX IN RETENTION OF PITCH IN AUDITORY SHORT-TERM MEMORY

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SUMMARY

In order to investigate the neural mechanisms underlying short-term memory for auditory information, 71 patients who had undergone focal excision from the left or right temporal or right frontal or fronto-temporal area for the relief of intractable epilepsy were tested, together with 18 normal control subjects, on a task requiring short-term retention of tonal pitch. In the control condition, a target tone was presented, followed 1650 ms later by a comparison tone, and subjects determined whether the two had the same pitch or not. In the interference condition a series of interpolated tones was presented between target and comparison tone. Results indicated that there was no significant impairment in any patient group on the control task. In the interference task there was a significant deficit in retention of tonal information in the patients with right temporal-lobe damage, as well as in those with lesions in the right frontal lobe, and in the right frontal and temporal area. Patients with left temporal-lobe excisions did not demonstrate a significant deficit. These findings are in agreement with research on non-human primates suggesting that structures in the superior temporal gyrus are important in retaining auditory information over short time spans, and further indicate that the human right temporal area is specialized for this function.

INTRODUCTION

Several lines of evidence suggest that a specialized neural mechanism exists for auditory short-term memory, and that it is linked to the function of the auditory association cortex in the superior temporal gyrus. Behavioural studies with monkeys have shown that lesions of the superior temporal cortex, sparing the primary auditory region, lead to impairments in the ability to retain auditory information in a delayed matching-to-sample task (Stepien *et al.*, 1960; Colombo *et al.*, 1990). This deficit appears to be selective to the auditory system, since such animals do not experience difficulty with similar visual discrimination tasks. Moreover, damage to this region does not lead to generalized auditory processing deficits because basic auditory discrimination ability is retained, even with large bilateral lesions of auditory cortex (Jerison and Neff, 1953; Heffner and Masterton, 1978).

Experimental psychology studies using normal human subjects have also provided convincing evidence for a specialized auditory memory system. Several investigators (Harris, 1952; Wickelgren, 1966, 1969) have found that pitch information decays slowly in the absence of interference, but Deutsch (1970) and Massaro (1970) reported that discriminating the pitch of 2 tones becomes difficult when the time interval between them is filled by irrelevant distracting tones. More importantly, when the distracting material consists of spoken digits there is no decrement in performance (Deutsch, 1970), indicating that the system that retains tonal information is separate from the one

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responsible for processing auditory verbal information. Other authors have found that an interpolated noise burst has no effect on tonal discrimination (Zatorre, 1983), although this depends on the specific task parameters used (Massaro, 1970). There is also recent evidence that pitch is processed independently of timbre in auditory short-term memory (Semal and Demany, 1991). In addition, Deutsch (1972) has found that the degree of pitch similarity between the interfering material and the target influences performance in a systematic fashion. On the basis of these and other data, she has proposed the existence of a specialized system for processing and retaining tonal pitch information (Deutsch, 1982).

To date, there has not been much work attempting to probe the neural substrate for human auditory short-term memory. However, there is evidence suggesting that there may be at least partially separate mechanisms for processing different types of auditory materials. For example, following lesions of the left hippocampal region, auditory verbal information is rapidly lost when an interfering task must be performed before recall (Corsi, 1972). Retention of tonal information may depend more on right-hemisphere function, although the evidence suggests that both hemispheres may be involved to some degree. In several studies involving paired comparisons of auditory tonal materials (Milner, 1962; Zatorre, 1985; Samson and Zatorre, 1988) it has been reported that right temporal-lobe lesions produce the greatest impairment. However, damage involving the primary auditory cortex on either side may lead to reduced performance in discrimination tasks (Zatorre, 1985; Samson and Zatorre, 1988), raising the possibility that this may have been due to an impairment in the ability to retain the stimuli in some short-term store.

To our knowledge, there has been only one attempt (Prisko, 1963) to directly examine retention of tonal stimuli in patients with unilateral temporal or frontal lobe lesions. Prisko found that neither left nor right anterior temporal lobectomy resulted in a decrement of tonal short-term retention, although there was a deficit in a group of patients with large excisions in the right hemisphere, including the temporal lobe and parts of the parietal and occipital lobes. Her task probably did not permit an adequate assessment of auditory tonal retention, however, since the interference was presented in a different modality from that of the to-be-remembered stimulus. This may explain the lack of effect of anterior temporal lesions in this study.

Because of the scarcity of relevant data, we wished to examine directly the role of the temporal lobes in auditory retention of tonal materials. For this purpose, we tested subjects with unilateral temporal lobectomy on a pitch discrimination task with or without tonal interference. We hypothesized that damage to the temporal neocortex on the right side should lead to deficits in discriminating the pitch of 2 tones only when the tones are separated by distracting materials. We also wished to examine the possible contribution of the hippocampal structures and primary auditory cortex to this task.

METHOD

Subjects

Seventy-one patients who had undergone focal unilateral cerebral excision for the relief of intractable epilepsy, and 18 normal control subjects were tested. All subjects were right-handed as determined by a handedness questionnaire (Crovitz and Zener, 1962), except for 3 patients in the right temporal lobe group and 1 in the right frontotemporal group who were left-handed. All of these left-handed patients had been shown to have left-hemisphere language representation via the intracarotid Sodium Amytal test (Branch *et al.*, 1964). In all the patients the pre-operative cerebral lesion had been well lateralized and, except where noted below, all lesions were static and atrophic. Patients were excluded from study if they presented atypical speech representation, had known damage outside the region of surgical excision, had a fast-growing tumour, or had a Full-Scale WAIS-R IQ under 75.

The normal control (NC) subjects were chosen to match the patient groups as much as possible in terms of age and educational background. Data regarding the subjects' age, sex distribution, number of years of education and IQ ratings are given in Table 1. There was no difference among the subject groups in terms of age [F(4,81) = 1.29, $P > 0.10$], years of education [F(4,81) = 0.49], or in Full-Scale IQ ratings [F(3,63) = 0.58]. In addition, the average digit span score from the WAIS-R is given in Table 1. This score gives an approximate measure of verbal short-term retention, and did not differ across the 4 patient groups [F(3,61) = 2.27, $P > 0.05$]. All were close to the normative average score of 7 digits. None of the subjects reported having absolute pitch, nor were any of them professional musicians.

TABLE 1 CHARACTERISTICS OF SUBJECTS

Group	*Sex* *M*	*F*	*Mean age (yrs)*	*Education (yrs)*	*FSIQ*	*Digit span*
NC	13	5	27.0 (13–43)	14.4 (8–20)	–	–
LT	14	12	28.3 (15–50)	12.8 (9–18)	105 (81–135)	7.1
RT	12	14	29.3 (16–44)	13.0 (8–19)	109 (87–127)	6.3
RF	10	3	31.4 (20–47)	13.3 (7–20)	109 (88–132)	6.3
RFT	5	2	25.7 (19–35)	13.8 (10–16)	104 (83–124)	6.9

FSIQ = Full scale WAIS-R IQ; ranges are in parentheses for each group of subjects.

The patients were divided according to side and extent of excision. Twenty-six patients had undergone right temporal (RT) lobectomy, including in all cases the uncus and amygdala. Of these, 18 had had a relatively limited excision of the hippocampus and parahippocampal gyrus (1.5 cm or less, as determined by the neurosurgeon at the time of operation), and 8 had had a more extensive hippocampal resection. The excision extended into Heschl's gyri in half of the subjects in the RT group, the other half having a more anterior resection that spared this region.

There were 26 subjects who had undergone left-temporal (LT) lobectomy. In 22 of these the hippocampal resection was limited, and in the remaining 4 the excision of the hippocampal region was extensive. The resection encroached onto Heschl's gyri in 13 of the patients in the LT group, whereas this region was spared in the remaining 13 subjects.

Two additional groups of patients were tested. Twelve patients had undergone a cortical removal confined to the right frontal (RF) lobe. The lesions in this group were somewhat heterogeneous, with excisions ranging from limited removals involving only the parasagittal or orbitofrontal regions, to more radical frontal lobectomies. In addition, a group of 7 patients was included who had combined lesions of the right frontal and temporal (RFT) lobe. Brain maps showing estimated extent of removal in the subjects in these latter 2 groups are shown in Figs. 1 and 2 No subjects with lesions confined to the left frontal (LF) lobe who fulfilled the other selection criteria were available for testing.

Stimuli and procedure

Tones were constructed by means of digital synthesis on an Apple personal computer. All tones were created with a sawtooth waveform comprising 12 successive harmonics. The target and comparison tones were of 325 ms duration. Interference tones were identical to these tones except that they were only 162.5 ms in duration.

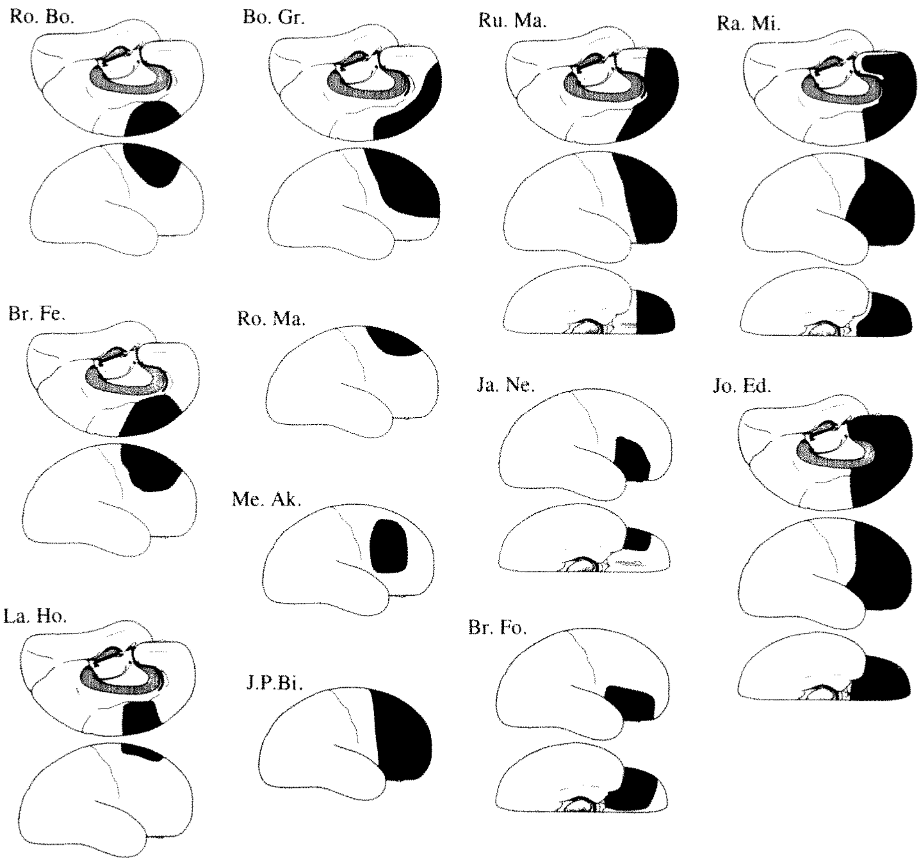
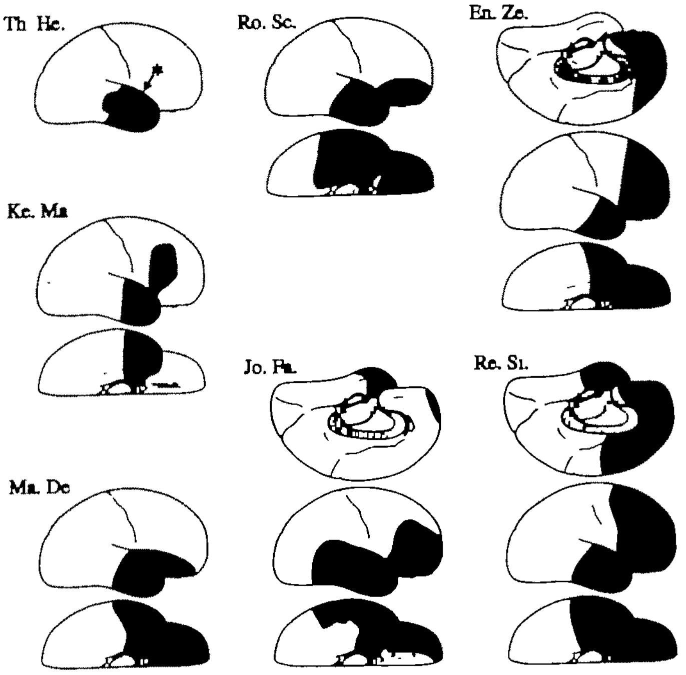


FIG. 1. Brain maps showing estimated extent of removal (in black) based on surgeon's drawing in the patients with excision from the right frontal cortex (group RF). Where appropriate, 3 views of the brain are shown, with the medial aspect above, the lateral aspect in the middle and the ventral surface below (e.g. case Ru. Ma.). For some cases, only 2 views were appropriate or available, and for other cases the lateral view alone is shown.

Each subject was tested individually on 2 separate tasks, a control and an interference task, performed in that order. In the control task, a target tone was presented, followed after a silent period of 1650 ms by a comparison tone which was either identical to the target or differed in pitch. There were 24 trials, half of which were same items, and the other half different items. When the tones differed the comparison tone was always of a higher pitch than the target, and it could differ by 1 of 3 pitch levels: 1, 2 or 3 whole-tone steps (corresponding to frequency ratios of 1.122, 1.259 and 1.413, respectively). These pitch differences were equally and randomly distributed in 4 trials each. Same or different items were also presented in a random order.

For the interference task, the stimulus parameters were identical to the control task, except that the time interval between the target and comparison tones was filled by 6 distractor tones. The series of distractor tones began 325 ms after the end of the target tone, and ended 325 ms before the onset of the comparison tone. No temporal gaps were placed between the 6 tones of the distractor series. Fig. 3 shows the stimulus configuration schematically.

The target tone for each stimulus pair was chosen randomly from the 12 notes of the equal-tempered chromatic scale between middle C (261.6 Hz) and B (493.9 Hz). All distractor tones (except for the one in second serial position) were chosen at random from the equal-tempered scale spanning 1 octave above



* Frontal opercular removal

FIG. 2 Brain maps showing estimated extent of removal (in black) based on surgeon's drawing in the patients with excision from the right frontal and temporal cortex (group RFT). *See* Fig 1 for explanation of the different views of the brain illustrated in this figure.

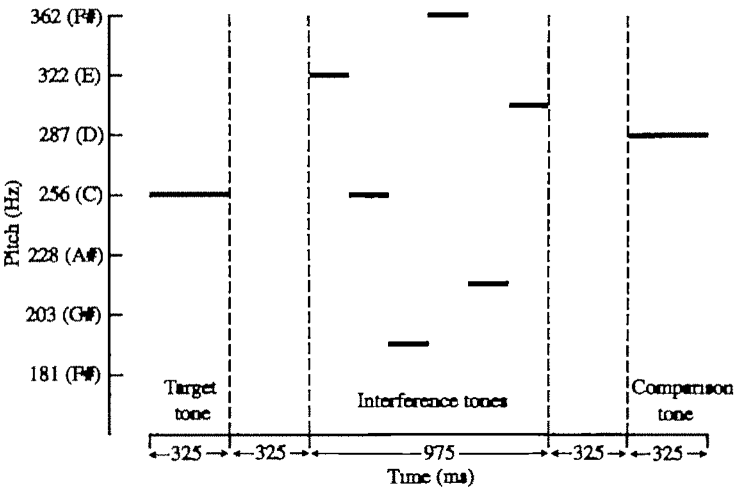


FIG. 3. Schematic diagram showing stimulus configuration Each dark line represents 1 tone.

and below the target tone, excluding any pitches which lay within a range 1 whole tone above or below the target. No distractor tones were repeated within any one series. In all, there were 72 trials, presented in random order: in 36 of them the comparison tone was identical to the target, and in the remaining 36 it differed. Within the 36 different trials, there were 12 trials each with pitch differences of 1, 2 or 3 whole tones.

For trials in which the target and comparison tones differed in pitch, the distractor tone in second serial position (termed the critical distractor tone), was chosen according to criteria similar to those used by Deutsch (1972): in one-third of these trials the critical distractor tone was identical in pitch to the first target tone, in another third of the trials it differed in pitch from the first target tone by 1 whole tone (either higher or lower), and in the remaining third of the trials it differed from the first target tone by more than 1 whole tone. In the case of trials containing identical target tones, the distractor tone in second serial position was chosen in the same way as the other distractors. The critical tone was placed in second serial position in order to allow comparison with the data of Deutsch (1972).

In the control task subjects were instructed to listen to the 2 tones and respond verbally whether the tones were same or different in pitch, and to guess if not sure. Two practice trials were given before beginning. For the interference task subjects were told that the 2 tones would be separated by a series of other tones, but that they were to ignore this interpolated series, and determine if the first and last tones were identical or not. Two practice trials were given before beginning, and subjects were encouraged to guess when not certain of the response.

The stimuli were recorded onto audio tape, and played through matched earphones (Telephonics TDH-39) at a sound pressure level of approximately 75 dB.

RESULTS

The dependent variable for all the parametric tests was the proportion of incorrect responses. The principal results are shown in Fig. 4, which plots overall percent errors for the control and interference tasks for each group of subjects. Inspection of the data suggests that patients in the RT, RF and RFT groups were impaired on the interference task, but not on the control task, whereas patients in the LT group were not deficient on either task. Although the mean error rate for the LT group seems somewhat elevated in the interference task, this was probably due to a few outliers in the distribution. These conclusions were borne out by several statistical analyses.

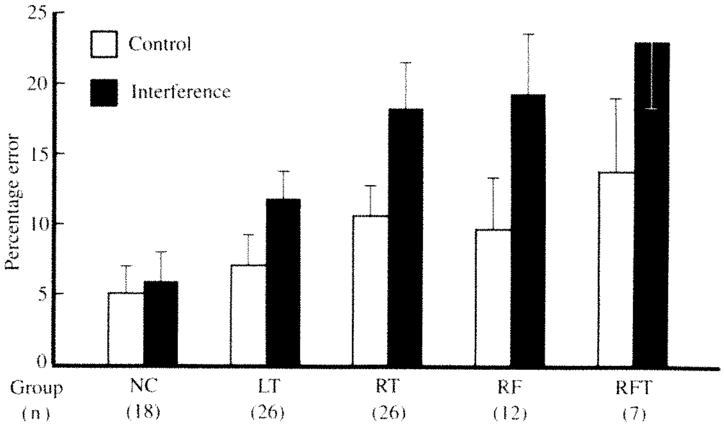


FIG. 4. Mean percentage correct pitch discrimination for each group of subjects in the control condition (no interference) and in the interference condition. One standard error of the mean is shown by error bars.

Parametric analysis of performance on interference vs control tasks

The first analysis of variance (ANOVA) examined the performance of each of the 5 groups of subjects on the 2 tasks, separately for same and different trials. The ANOVA therefore comprised 3 factors: Group, a between-subject factor, and 2 within-subject factors; Task (control vs interference); and Trial type (same vs different trials). This analysis yielded significant main effects of Group [F(4,84) = 2.57, $P < 0.05$], Task [F(1,84) = 47.58, $P < 0.0001$], and Trial type [F(1,84) = 46.73, $P < 0.0001$]. In addition, there were significant interactions of Task by Group [F(4,84) = 3.64, $P < 0.009$] and Task by Trial type [F(1,84) = 6.03, $P < 0.02$]. The main effects of Task and Trial type are clearly due to the fact that the interference task resulted in many more errors than the control task, and that most errors occurred on different rather than on same trials. The interaction of Task by Trial type reflects the largest proportion of errors on the different trials of the interference task.

The most interesting results bear on the significant effects involving the Group factor. The 3 groups with the highest proportion of errors were RT, RF and RFT. Because the Group effect interacted with the Task variable, we examined performance of each subject group separately on each task by means of Newman-Keuls comparisons. These comparisons revealed that none of the patient groups differed significantly ($P < 0.05$) from the NC group on the control task, but on the interference task the RT, RF and RFT groups were all significantly worse than the NC group ($P < 0.01$ in all cases); in contrast, the LT group did not differ significantly from the NC group (*see* Fig. 4).

A similar result is found comparing performance within each group for the 2 tasks. Newman-Keuls contrasts showed that whereas there was no statistically significant increase in errors between control and interference tasks for the NC and LT groups, there were more errors on the interference task as compared with the control task for the RT, RF and RFT groups ($P < 0.05$).

Note that there was no interaction of Group by Trial type, meaning that performance was equally affected for same and different trials. This finding argues against the possibility that the impairments observed could have been due to a change in response bias, such that more false alarms might have been produced, for example, by one or more groups.

Non-parametric analyses of error scores

In order to confirm the primary findings, we carried out 2 supplementary non-parametric analyses of the data. These analyses are important because we observed that the distributions were generally non-symmetrical with most subjects in each group performing near ceiling, but with some performing relatively poorly in each group. We therefore wanted to verify the validity of the parametric tests by examining performance on distribution-free statistics. The first of these analyses permits us to examine more closely how each individual subject performed, rather than examining only the mean performance of each group as was done with the parametric analysis. In order to verify that more subjects within the RT group performed more poorly on the interference task as compared with the NC and LT groups, we counted how many subjects exceeded an error criterion of 15% errors on the interference task, which is equivalent to 1 standard deviation above the mean of the NC group. Whereas only 4 of 18 NC subjects performed more poorly than this criterion, nearly two-thirds of the subjects in the RT group (17 of 26) exceeded 15% errors, which is a highly significant difference by Fisher's exact test ($P < 0.005$). In contrast, only 8 LT patients were above the criterion, which, compared with the NC subjects, does not even approach significance (Fisher's exact test, $P = 0.39$). In addition, the distribution of subjects was significantly different between LT and RT groups (Fisher's exact test, $P < 0.02$), again confirming the RT group's poor performance. On the other hand, the same analysis applied to the data from the control condition did not yield significant differences between any of the groups, confirming the lack of deficit on this task.

A second non-parametric analysis involves rank-ordering the performance of each individual regardless of which group they belong to, and then determining if the ranks are consistently higher in one group. This approach has the advantage of conserving ordinal information, does not depend on the data being distributed in any particular way, and is less affected by outliers than a parametric test. A Kruskal-Wallis analysis of ranks was performed on the percent error data for both control and interference conditions. This yielded a highly significant group difference for the interference condition ($H = 16.6$, $P < 0.005$), but no significant group differences for the control condition ($H = 4.5$, $P > 0.30$), in agreement with the previous analyses. Finally, pairwise comparisons between groups were carried out via the Mann-Whitney test to verify that the ranked data indicated the same pattern of deficits for each group as had been found with the other statistics. This was indeed the case, with no significant group differences emerging for the control task, and with significant differences between the NC group and the RT, RF and RFT groups on the interference task (respectively: $U = 97$, $P < 0.002$; $U = 49$, $P < 0.02$; $U = 13.5$, $P < 0.003$).

Thus, both parametric and non-parametric analyses are in complete agreement that there was no statistically significant difference in performance on the control task, despite some trend toward increased error rate in some of the groups. The analyses are also in accord that there is an impairment specifically on the interference condition in groups RT, RF and RFT, but that there is no impairment on any of the measures used for the LT group.

Analysis of effect of pitch difference between target and comparison

A second parametric ANOVA was performed to examine performance of each group as a function of pitch difference between the tones. For this analysis only the data from the interference task were used. The factors were Group, as before, and Pitch difference: zero (same trials), 1, 2 or 3 whole tones. This analysis yielded a significant effect of Group [$F(4,84) = 4.04$, $P < 0.005$], as well as a significant effect of Pitch difference [$F(3,252) = 43.83$, $P < 0.0001$], but no interaction effect. Not surprisingly, Newman-Keuls *post hoc* tests showed that the greatest number of errors (average across all subjects of 31.4%) was committed by all groups when the pitch difference was 1 whole tone, with significantly ($P < 0.01$) fewer errors (17.9%) when the pitch difference was 2, and fewer still (9.8%) with the largest pitch difference of 3 whole tones ($P < 0.01$). The proportion of errors in the case of 3 whole-tone pitch difference was not different from the proportion of errors for same trials (8.8%).

Analysis of effect of pitch of critical distractor tone

The next analysis investigated the effect of the distance between the pitch of the critical interference tone, the tone in second serial position within the interference series, and the target tone. For this ANOVA once again only the data from the interference task were used. The factors were Group and Pitch distance of critical tone (0, 1 or more than 1 whole tone from the target, alone with same items). Once again the analysis yielded a significant group effect [F(4,84) = 3.66, $P < 0.01$], and an effect of the pitch distance of the critical tone [F(3,252) = 49.04, $P < 0.0001$], but no significant interaction of these two factors. *Post-hoc* tests showed that the lowest error rate for all subjects was obtained on same trials; in addition, there were significantly more errors on different trials in which the critical distractor tone was 1 or more whole tones removed from the target, as compared with different trials in which the critical tone was identical to the target ($P < 0.01$). These results are shown in Table 2.

TABLE 2 MEAN PERCENT ERROR RATE FOR EACH GROUP OF SUBJECTS IN INTERFERENCE TASK AS A FUNCTION OF TRIAL TYPE AND PITCH DISTANCE BETWEEN TARGET TONE AND SECOND INTERPOLATED TONE

		Trial type			
Group		*Same*	*Different*		
	*Distance**	*>1*	*0*	*1*	*>1*
NC		3.1	6.5	12.5	14.4
		(7.4)	(11.3)	(16.7)	(17.5)
LT		6.7	12.2	17.9	21.2
		(11.1)	(15.0)	(17.6)	(20.4)
RT		12.2	21.8	27.6	26.6
		(14.0)	(20.2)	(20.3)	(18.9)
RF		12.7	24.3	30.6	32.6
		(13.8)	(22.4)	(20.8)	(22.4)
RFT		12.3	31.0	34.5	39.3
		(15.3)	(13.1)	(20.6)	(19.3)

*In whole-tone steps; standard deviation in parenthesis.

Analysis of lesion extent and location in the temporal lobe

Finally, we undertook to study the effect of lesion extent and location within the temporal lobe groups. For this purpose, the subjects in the LT and RT groups were subdivided according to whether the excision spared or included Heschl's gyri, and according to whether the resection in the hippocampal region was classed as limited or extensive. The ANOVA thus included 3 between-subject factors: Side of lesion (left or right), Heschl's gyrus (spared or excised) and Hippocampus (limited or extensive removal). Additionally, the same within-subject factors as in the first ANOVA were included: Task (control vs interference) and Trial type (same vs different). The only significant effects obtained in this ANOVA were replications of the previous analysis, since both Task [F(1,39) = 14.66, $P = 0.0005$] and Trial type [F(1,39) = 16.17, $P = 0.0003$] were significant. No other main effects or interactions were noted, indicating that there was no significant effect of either hippocampal or Heschl's gyri excision.

DISCUSSION

In keeping with the predictions, the results clearly showed that retention of tonal information is disturbed following damage to the right temporal neocortex, but that this impairment is specific to the condition when the delay period is filled with distracting tonal material. These data suggest that regions within the human right temporal lobe are important in maintaining auditory information in a short-term memory store. When interfering sounds are presented, this presumably taxes the ability of the damaged system beyond the point that it can reliably maintain the first stimulus in the pair to permit comparison with the final stimulus. The group of patients with excision in the left temporal lobe did not demonstrate a reliable impairment on any statistic performed, despite having a slightly elevated mean error score. It should be pointed out that there was considerable individual variation in the performance of the interference task, even in the normal control subjects, although most subjects performed relatively well. [One reason for greater variability of performance in the present study as compared with previous ones is that in many such experiments (e.g. Deutsch, 1972) only subjects who exceed a 90% correct criterion on a control pitch interference task are retained. This procedure effectively cuts off any outliers in the distribution, thereby reducing the variance. In the present study, no such screening could be carried out, as our purpose was specifically to document poor performance.] The non-significant increase in errors in the LT group would appear to be due to a few outlying subjects who performed poorly, and not to a general characteristic of patients with this lesion. This conclusion is borne out by the non-parametric analyses, which demonstrated clear differences between the distributions of error scores between RT and NC groups, but not between LT and NC groups. Moreover, the number of RT subjects exceeding the error criterion of 15% is significantly greater than the number of LT subjects exceeding this same criterion. Thus, although some individual patients in the LT group may have been impaired, we have no convincing evidence for a consistent deficit.

The cortical fields in the temporal lobe that are responsive to auditory stimulation may be subdivided into several distinct areas, based on cytoarchitectonic and physiological criteria. Several of these regions are believed to have a tonotopic representation (for a review, *see* Brugge and Reale, 1985). The primary auditory cortex, which in the human brain is believed to lie within the transverse gyri of Heschl (Celesia, 1976; Galaburda and Sanides, 1980; Liegeois-Chauvel *et al.*, 1991), is surrounded by several other auditory fields, many of which receive input directly from the medial geniculate nucleus in addition to corticocortical connections from the primary region (FitzPatrick and Imig, 1982). In an anterior temporal lobectomy several of these secondary auditory regions would most likely be excised. Given our results, we would conclude that retention of auditory information for brief periods of time would be one function of these areas within the right temporal lobe. We did not find that damage of Heschl's gyri or the hippocampal region produced any additional deleterious effect in the right temporal lobe group; rather, anterior temporal lobectomy was sufficient to bring out the deficit. This finding is unlikely to be the result of a simple floor effect, as performance was not near chance level in most conditions tested. We interpret this result as evidence that the critical locus of damage within the temporal lobe is most probably the neocortex of the first temporal gyrus. This conclusion is supported by the recent study of Colombo *et al.* (1990) who reported that bilateral lesions limited to the superior temporal gyrus of monkeys, but sparing the primary auditory cortex, lead to auditory retention deficits.

The human neuropsychological literature indicates that the ability to distinguish 2 tones differing in frequency is not affected by unilateral temporal lobectomy (Milner, 1962; Zatorre, 1988), suggesting that such discriminations do not depend on the integrity of either the primary or association auditory cortices. Similar findings have been reported in the animal literature (Evarts, 1952; Jerison and Neff, 1953; Heffner and Masterton, 1978; Colombo *et al.*, 1990). [Interestingly, one study that did report deficits in frequency discrimination after temporal lobe lesions in monkeys (Massopust *et al.*, 1971) used a paradigm that likely involves a high short-term memory load (Heffner and Heffner, 1990).] The present results are in accord with this conclusion, as no consistent deficit was obtained for any subject group in the control condition. Even though the mean error rates were somewhat elevated for some of the patient groups in the control condition, this was primarily due to poor scores by a few individuals, and none of the statistical procedures used produced any evidence of a difference between groups beyond what might be expected by chance. However, we have previously found that pitch perception can be impaired in the case of complex tones with no fundamental frequency component, but only when the excision includes part of the right Heschl's gyri (Zatorre, 1988). These findings point to an interesting dissociation, since in the present study retention of tonal information is disturbed following an anterior right temporal lobectomy, but no exacerbation is observed if the excision encroaches onto Heschl's gyri. Thus, it would appear that there is a certain degree of segregation of function within the right temporal lobe, with pitch extraction mechanisms dependent more on cortical systems in and around Heschl's gyri, but tonal short-term retention mechanisms dependent on the secondary auditory cortical areas.

It is also notable that hippocampal excision did not bring out any further deficit in the right temporal-lobe group. In this respect Wickelgren's (1969) findings are of considerable interest. He proposed that the rate of decay of pitch information in a retention task could be explained by the existence of 2 memory traces, a short-term one with a decay constant of about 5 s, and an intermediate-term trace with a decay constant on the order of 40 s or more. Of greatest relevance to the present results in Wickelgren's (1968) study of the patient H.M., who underwent bilateral hippocampal resection, and who subsequently demonstrated very severe anterograde amnesia (Scoville and Milner, 1957). H.M.'s pitch retention function showed a normal short-term decay rate, but no intermediate-term component, suggesting that hippocampal damage does not affect short-term auditory memory, but does eliminate the ability to form intermediate-term memory traces. This suggestion is in accord with our findings to the extent that our paradigm probably involves primarily a short-term retention component, and therefore hippocampal damage would not be expected to have any effect. Thus, whereas hippocampal damage, at least in the case of bilateral excision, affects intermediate-term but not short-term auditory retention, right temporal lobectomy affects short-term retention, with no further deficit after large hippocampal excision. This dissociation of function adds further evidence to our conclusion that it is the temporal neocortex of the right hemisphere that is primarily involved in pitch memory over short retention intervals.

Within the group of normal control subjects, it was unexpectedly found that the interference task did not produce a significantly larger proportion of errors than the control task. This result would appear to contradict Deutsch's (1970, 1972) findings, but it can most likely be explained in terms of two important differences in the experimental procedure. First, in Deutsch's (1972) version of the interference task, the target and comparison tones were only separated by a semitone, so that the pitch discrimination itself is more difficult than in the version used in the present study. (In the present study, differences of 1, 2 and 3 whole tones were used because in pilot testing it had been determined that one-semitone discrimination would prove too difficult for many of our subjects.) The second major difference is in the temporal parameters of the interference stimuli: whereas Deutsch's target and comparison tones were separated by 5 s, our delay interval was much shorter at 1650 ms. Moreover, in her study the 6 interpolated tones occur at equally spaced intervals after the target tone, but in our case there was a gap before the onset of the interpolated tones, which were all played contiguously. These temporal differences probably render our interference tones more easily separable from the target, and therefore less effective as interference. In any case, the interference stimuli were clearly effective in the case of patients in the RT, RF and RFT groups, indicating that these patients have difficulty retaining information in the presence of interfering stimuli even when the interference is quite mild by the standards of the NC group. It is to be expected that the deficits would have been correspondingly larger if a more taxing interference task had been used.

Although the interfering effect of the interpolated tones was very weak in the normal control subjects, it is notable that another of Deutsch's (1972) findings was replicated: we found that all subjects performed better when the interference tone in second serial position was identical to the target tone than when it differed by 1 or more whole-tone steps (Table 2). This facilitation is important in that it reflects interactions in the pitch memory storage system. Since all patient groups displayed the same tendencies for facilitation or interference as a function of pitch of the critical interference tone, we may conclude that the deficit uncovered does not lie at the level of encoding or organization of the pitch information itself. Rather, it seems more likely that the deficit, at least in the case of patients with right temporal lobe lesions, is probably due to a faster than normal decay, or to a heightened susceptibility to interference.

A somewhat unexpected finding of the present study was that lesions involving the right frontal lobe affect performance on this task. A number of other studies have reported deficits in auditory discrimination tasks following frontal lobe damage both in monkeys (e.g. Blum, 1952; Gross and Weiskrantz, 1962; Iversen and Mishkin, 1973) and humans (Prisko, 1963) using various types of stimuli and procedures. On the other hand, Zatorre (1985) did not find deficient performance on a melodic discrimination task in patients with left or right frontal lobectomy. Petrides and Pandya (1988) have documented the anatomical input from the superior temporal gyrus to various regions within the frontal lobe, and it may be that frontal lesions disrupt some aspect of auditory processing important in certain types of discrimination tasks. An alternative hypothesis is that the nature of the impairment in the RF group may be somewhat different from that of the RT group. Specifically, it may be that some of the patients with damage to the right frontal area have difficulty inhibiting incorrect responses under the delayed comparison paradigm used here. This explanation would be more in keeping with the widely held concept that the frontal lobes are involved in the regulation of behaviour in response to input from all sensory modalities, as opposed to a specific role in auditory processing (Milner and Petrides, 1984; Stuss and Benson, 1986; Petrides and Pandya, 1988). A related explanation that should be considered is that right frontal lobe lesions disrupt the vigilance necessary to perform well on the task (Wilkins *et al.*, 1987). Thus, the poor performance may have been due to problems in sustaining attention during the relatively monotonous interference task.

One additional interpretation of the RF lobe effect should be considered. It is possible that short-term auditory memory involves a distributed network in which connections between pre-frontal and temporal cortices serve to maintain information over filled delays (Chavis and Pandya, 1976; Perry, 1992). Such a model has been proposed for visuospatial working memory (Goldman-Rakic, 1988), and may be generalizable to other modalities. One piece of evidence supporting this interpretation comes from a recent positron emission tomography study measuring cerebral blood flow in normal subjects during the performance of a pitch judgement task (Zatorre *et al.*, 1991). The results indicated activation of an inferior RF site during this task, which would be consistent with the idea that specific areas within the right prefrontal cortex serve an important role in maintenance of pitch information, presumably through interaction with specialized secondary auditory cortical regions in the superior temporal gyrus.

The lateralized nature of the deficit obtained in this study gives further support to the relatively large body of evidence indicating a privileged role for the right cerebral hemisphere in certain aspects of processing musical sounds (Milner, 1962; Shankweiler, 1966; Zatorre, 1985; Samson and Zatorre, 1988; Sidtis and Volpe, 1988). It is interesting to consider that most of these studies have used various forms of a discrimination task, in which 2 or more stimuli must be compared, necessitating some type of short-term retention. The deficit described in the present study might be a contributing factor to some of these reported deficits, at least under conditions of relatively high load on short-term memory. This need not be confined to situations in which interference is present. It is entirely possible that the load on the short-term retention mechanism might be increased simply by making the stimulus to be retained more complex. Thus, there may be at least a partial contribution of auditory retention impairments to the melodic processing deficits described in the literature. Note, however, that an impairment in short-term retention cannot be responsible for the specific deleterious effect of Heschl's gyri excision from either the right or left side observed by Zatorre (1985) and Samson and Zatorre (1988) on melodic discrimination, since the deficit described in the present research is not related to Heschl's gyri excision, and is limited to right temporal-lobe damage.

A question of interest for future research is whether the deficit we have observed is generalizable to retention of other auditory signals, or whether it represents a specialization of the right temporal lobe for retention of tonal information. The evidence from the cognitive psychology literature would suggest that there are multiple storage systems that are, at least to a large extent, independent from one another (Deutsch, 1970), and the present data may be interpreted as reflecting the existence of a right temporal lobe system specialized for tonal retention. An alternative way to conceptualize these different retention mechanisms is in terms of the type of memory coding that may take place. In the case of tones, the information is most likely encoded in terms of a relatively unprocessed auditory sensory code, rather than a more highly elaborated verbal or visual imaginal code, for example. It is an interesting possibility that the right superior temporal gyrus may be specialized for retaining information for a brief period of time in the form of an auditory sensory code after initial processing has taken place but prior to further processing by other neural subsystems. (Initial processing, which is assumed to take place in the primary auditory cortex as well as in subcortical auditory centres, might include the computation of such parameters of the signal as its pitch, duration and spectral shape.)

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REFERENCES

BLUM RA (1952) Effects of subtotal lesions of frontal granular cortex on delayed reaction in monkeys. *Archives of Neurology and Psychiatry, Chicago,* **67,** 375–386.

BRANCH C, MILNER B, RASMUSSEN T (1964) Intracarotid Sodium Amytal for the lateralization of cerebral speech dominance: observations in 123 patients. *Journal of Neurosurgery,* **21,** 399–405.

BRUGGE JF, REALE RA (1985) Auditory cortex. In: *Cerebral Cortex,* Volume 4. Edited by A. Peters and E. G. Jones. New York and London: Plenum Press, pp. 229–271.

CELESIA GG (1976) Organization of auditory cortical areas in man. *Brain,* **99,** 403–414.

CHAVIS D, PANDYA DN (1976) Further observations on corticofrontal pathways in the rhesus monkey. *Brain Research,* **117,** 369–386.

COLOMBO M, D'AMATO MR, RODMAN HR, GROSS CG (1990) Auditory association cortex lesions impair auditory short-term memory in monkeys. *Science,* **247,** 336–338.

CORSI P (1972) *Human Memory and the Medial Temporal Regions of the Brain.* Doctoral thesis, McGill University, Montreal.

CROVITZ HF, ZENER K (1962) A group-test for assessing hand- and eye-dominance. *American Journal of Psychology,* **75,** 271–276.

DEUTSCH D (1970) Tones and numbers: specificity of interference in immediate memory. *Science,* **168,** 1604–1605.

DEUTSCH D (1972) Mapping of interactions in the pitch memory store. *Science,* **175,** 1020–1022.

DEUTSCH D (1982) The processing of pitch combinations. In: *The Psychology of Music.* Edited by D. Deutsch. New York and London: Academic Press, pp. 271–316.

EVARTS EV (1952) Effect of auditory cortex ablation on frequency discrimination in monkey. *Journal of Neurophysiology,* **15,** 443–448.

FITZPATRICK KA, IMIG TJ (1982) Organization of auditory connections: the primate auditory cortex. In: *Cortical Sensory Organization,* Volume 3. Edited by C. N. Woolsey. Clifton, NJ: Humana Press, pp. 71–109.

GALABURDA A, SANIDES F (1980) Cytoarchitectonic organization of the human auditory cortex. *Journal of Comparative Neurology,* **190,** 597–610.

GOLDMAN-RAKIC PS (1988) Topography of cognition: parallel distributed networks in primate association cortex. *Annual Review of Neuroscience,* **11,** 137–156.

GROSS CG, WEISKRANTZ L (1962) Evidence for dissociation of impairment on auditory discrimination and delayed response following lateral frontal lesions in monkeys. *Experimental Neurology,* **5,** 453–476.

HARRIS JD (1952) The decline of pitch discrimination with time. *Journal of Experimental Psychology,* **43,** 96–99.

HEFFNER HE, MASTERTON B (1978) Contribution of auditory cortex to hearing in the monkey (*Macaca mulatta*). In: *Recent Advances in Primatology,* Volume 1: *Behaviour.* Edited by D. J. Chivers and J. Herbert. London: Academic Press, pp. 735–754.

HEFFNER HE, HEFFNER RS (1990) Role of primate auditory cortex in hearing. In: *Comparative Perception,* Volume II: *Communication.* Edited by W. Stebbins and M. Berkley. New York: John Wiley, pp. 279–310.

IVERSEN SD, MISHKIN M (1973) Comparison of superior temporal and inferior prefrontal lesions on auditory and non-auditory tasks in rhesus monkeys. *Brain Research, Amsterdam,* **55,** 355–367.

JERISON HJ, NEFF WD (1953) Effect of cortical ablation in the monkey on discrimination of auditory patterns. *Federation Proceedings,* **12,** 73–74.

LIEGEOIS-CHAUVEL C, MUSOLINO A, CHAUVEL P (1991) Localization of the primary auditory area in man. *Brain*, **114**, 139–153.

MASSARO DW (1970) Retroactive interference in short-term recognition memory for pitch. *Journal of Experimental Psychology*, **83**, 32–39.

MASSOPUST LC, WOLIN LR, FROST V (1971) Frequency discrimination thresholds following auditory cortex ablations in the monkey. *Journal of Auditory Research*, **11**, 227–233.

MILNER B (1962) Laterality effects in audition. In: *Interhemispheric Relations and Cerebral Dominance*. Edited by V. B. Mountcastle. Baltimore: Johns Hopkins Press, pp. 177–195.

MILNER B, PETRIDES M (1984) Behavioural effects of frontal-lobe lesions in man. *Trends in Neurosciences*, **7**, 403–407.

PERRY D (1992) A cognitive neuropsychological analysis of melody recall. *Contemporary Music Review*. In press.

PETRIDES M, PANDYA DN (1988) Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *Journal of Comparative Neurology*, **273**, 52–66.

PRISKO L-H (1963) *Short-term Memory in Focal Cerebral Damage*. Doctoral thesis, McGill University, Montreal

SAMSON S, ZATORRE RJ (1988) Melodic and harmonic discrimination following unilateral cerebral excision. *Brain and Cognition*, **7**, 348–360.

SCOVILLE WB, MILNER B (1957) Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry*, **20**, 11–21.

SEMAL C, DEMANY L (1991) Dissociation of pitch from timbre in auditory short-term memory. *Journal of the Acoustical Society of America*, **89**, 2404–2410.

SHANKWEILER D (1966) Effects of temporal-lobe damage on perception of dichotically presented melodies. *Journal of Comparative and Physiological Psychology*, **62**, 115–119.

SIDTIS JJ, VOLPE BT (1988) Selective loss of complex-pitch or speech discrimination after unilateral lesion. *Brain and Language*, **34**, 235–245.

STEPIEN LS, CORDEAU JP, RASMUSSEN T (1960) The effect of temporal lobe and hippocampal lesions on auditory and visual recent memory in monkeys. *Brain*, **83**, 470–489.

STUSS DT, BENSON DF (1986) *The Frontal Lobes*. New York: Raven Press.

WICKELGREN WA (1966) Consolidation and retroactive interference in short-term recognition memory for pitch. *Journal of Experimental Psychology*, **72**, 250–259.

WICKELGREN WA (1968) Sparing of short-term memory in an amnesic patient: implications for strength theory of memory. *Neuropsychologia*, **6**, 235–244.

WICKELGREN WA (1969) Associative strength theory of recognition memory for pitch. *Journal of Mathematical Psychology*, **6**, 13–61

WILKINS AJ, SHALLICE T, MCCARTHY R (1987) Frontal lesions and sustained attention. *Neuropsychologia*, **25**, 359–365.

ZATORRE RJ (1983) Category-boundary effects and speeded sorting with a harmonic musical-interval continuum: evidence for dual processing. *Journal of Experimental Psychology: Human Perception and Performance*, **9**, 739–752.

ZATORRE RJ (1985) Discrimination and recognition of tonal melodies after unilateral cerebral excisions. *Neuropsychologia*, **23**, 31–41.

ZATORRE RJ (1988) Pitch perception of complex tones and human temporal-lobe function. *Journal of the Acoustical Society of America*, **84**, 566–572.

ZATORRE RJ, EVANS AC, MEYER E (1991) Regional cerebral blood flow activation during processing of speech. *Third IBRO World Congress of Neuroscience*, p. 179.

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THE VISUAL DEFECT IN MULTIPLE SCLEROSIS AND OPTIC NEURITIS

A COMBINED PSYCHOPHYSICAL AND ELECTROPHYSIOLOGICAL INVESTIGATION

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SUMMARY

Chromatic and achromatic visual function were investigated using psychophysical and evoked potential techniques in 32 patients with multiple sclerosis (MS) or optic neuritis. There was no evidence for either chromatic or achromatic vision being selectively damaged. There was, however, some evidence that demyelination of the optic nerve causes a visual defect in which the transmission of high temporal frequencies is impaired. In some patients either a red or blue deficit was evident, but overall there was no evidence of a wavelength specific colour vision defect in our patient group. Reduction of chromatic sensitivity as determined psychophysically had a statistically significant correlation with the amplitude and latency of the chromatic visual evoked potential.

INTRODUCTION

Subtle abnormalities of colour vision are common in MS (Travis and Thompson, 1989) and optic neuritis (Griffen and Wray, 1978). A plausible explanation for this is that the optic nerve fibres which carry colour information are more prone to damage than those which carry luminance information. Multiple sclerosis is characterized by the destruction of myelin with relative preservation of axon continuity (McDonald, 1986). Acute unilateral optic neuritis in adults is one of the commonest manifestations of demyelinating disease (McDonald and Silberberg, 1986). Optic neuritis is the presenting feature in approximately 20% of cases of MS and, in the UK, occurs during the course of the illness in about 70% of cases (Shibasaki *et al.*, 1981; McDonald, 1983). Though demyelination could account for the rapid onset of vision loss in optic neuritis, reduction in oedema has been proposed as a mechanism for the recovery observed in some cases (Halliday and McDonald, 1977). Some optic nerve fibres remain impaired following the resolution of oedema and recovery of visual acuity (McDonald, 1983). This residual damage can be studied using non-invasive psychophysical and evoked potential techniques which therefore provide a means by which the physiological consequences of demyelination might be assessed. Such an approach can only be successful if the design of the stimuli takes into account the neurophysiology of the primary visual pathway.

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In primates two morphologically distinct systems of neurons exist within the primary visual pathway. Large retinal ganglion cells, A type (Leventhal *et al.*, 1981) or phasic (Gouras, 1968), project via thick optic nerve axons to the two magnocellular layers of the lateral geniculate nucleus (LGN), (Dreher *et al.*, 1976) and then to lamina 4C-alpha of the striate cortex (Hubel and Wiesel, 1972). The magnocellular, or M, pathway is composed of the inputs and outputs of the magnocellular layers of the LGN. Approximately 95% of these phasic M cells receive synergistic input from red and green cones, are insensitive to the colour of the stimulus and have a high contrast sensitivity; that is, they are sensitive to low contrast patterns (Wiesel and Hubel, 1966; Kaplan and Shapley, 1982). There is evidence that phasic cells can respond to red-green isoluminant borders (Lee *et al.*, 1989*a*). However, these responses are very much smaller for phasic cells than for tonic cells at low (10%) contrast (Lee *et al.*, 1989*b*) and are dependent upon the mean luminance of the stimulus (Lee *et al.*, 1989*a*). In addition, both onset and the offset of an isoluminant grating elicit similar responses from M cells, but the responses differ in polarity and amplitude for P cells, the off response being smaller. In general, the magnocellular (M) pathway, constituting 10% of the total number of optic nerve fibres, is regarded as subserving detection of low and medium spatial frequencies, movement and fast flicker (Livingstone and Hubel, 1987; Lee and Martin, 1989).

Small retinal ganglion cells, B type (Leventhal *et al.*, 1981) or tonic (Gouras, 1968), project via thin optic nerve axons to the four parvocellular layers of the LGN (De Monasterio and Gouras, 1975) and then to striate layer 4C-beta (Hubel and Wiesel, 1972). The parvocellular, or P, pathway consists of all inputs and outputs of the parvocellular layers of the LGN. Neurons in the parvocellular pathway represent around 80% of the total number of ganglion cells in the retina. The remaining 10% of optic nerve fibres project to mid-brain structures. Approximately 80% of P cells receive antagonistic inputs from red and green cones which means they exhibit colour selectivity (Wiesel and Hubel, 1966), but have a much lower contrast sensitivity than M cells (Kaplan and Shapley, 1982; Hicks *et al.*, 1983). The parvocellular pathway can therefore be considered to be the neural basis for the chromatic mechanism. Although there is considerable overlap in the range of the structural and functional properties of P and M pathways, stimuli can be chosen which are known to activate predominantly only one pathway.

The issue of selective damage to one or other pathway is pertinent to the understanding of the underlying pathology in MS. If, for example, fibre diameter, or a particularly high metabolic requirement, were predisposing factors then this should be manifest as a characteristic type of visual abnormality. In fact there is considerable variation in the form of visual defect encountered in MS. There are some indications from neurophysiological experiments which suggest that a demyelinating lesion may be more likely to affect some fibres than others. For example, using mice affected with Semliki Forest virus, Ikeda and Tansey (1986) showed that thin fibres are particularly susceptible to damage.

The impact of an episode of optic neuritis on the visual pathways and the resulting spatial (Regan *et al.*, 1981) and temporal (Heron *et al.*, 1974) distortions of perception have been investigated, but the precise nature of the mechanisms of visual loss remains obscure. Studies which have specifically investigated selective damage to either the luminance or chromatic pathways in optic neuritis and multiple sclerosis have reached conflicting conclusions. Alvarez *et al.* (1982) found a greater loss of luminance sensitivity than chromatic sensitivity using spectral sensitivity to separate the two mechanisms. Foster *et al.* (1985) concluded that there was no selective loss when they used a 15 min arc spot superimposed on an auxiliary field, the spatial extent of the auxiliary field and the colour of the target being manipulated to separate luminance and chromatic mechanisms. Fallowfield and Krauskopf (1984) used a 2 deg uniform field which was modulated in either saturation or luminance to show that chromatic thresholds were elevated more than luminance thresholds. Mullen and Plant (1986) measured chromatic and luminance contrast sensitivity using sinusoidal grating patterns of 6 deg angular subtense. They concluded that using their technique chromatic contrast sensitivity was more severely impaired than luminance contrast sensitivity. They point out, however, that the greater loss in chromatic than luminance contrast sensitivity seen in their patients is not necessarily selective to a particular detecting mechanism because the relative sensitivity of chromatic and achromatic systems may depend on the spatial and temporal characteristics of the stimulus employed.

In all these studies, much depends on the criteria used for defining luminance and chromatic function and the techniques used for their isolation. Inevitably this has led to wide differences of opinion as to which of the two aspects of visual function are affected most in multiple sclerosis. One of the main objectives of the present study was to throw light on this confusion.

In this study, separation of luminance and chromatic function is obtained using a spectral sensitivity technique first described by Sperling and Harwerth in 1971, later developed by King-Smith and Carden (1976) and used clinically by Alvarez *et al.* (1982). When increment thresholds for the detection of a small spectral light presented on a large white background are determined using 1 Hz presentation the three peaked function of sensitivity versus wavelength which is obtained has been shown to reflect the activity of chromatic (colour opponent) channels (Sperling and Harwerth, 1971). If the spectral light is presented at much higher rates (e.g. 25 Hz), its detection is considered to be mediated by thicker fibres with superior temporal properties. When observers set thresholds for the detection of the flicker of this target, the resulting single broad band function of sensitivity versus wavelength (King-Smith and Carden, 1976) is referred to as luminance sensitivity and is similar in shape to the standard CIE photopic luminosity function (Wyszecki and Stiles, 1967).

Separation of luminance and chromatic pathways can be obtained electrophysiologically by using stimuli which are known from neurophysiological studies to selectively activate P or M pathways. Although isoluminant red-green gratings can be detected by both M and P pathways (Lee *et al.*, 1989*b*), at low contrast there is evidence that only P pathways are activated (Tootell *et al.*, 1988). This approach was described by Carden *et al.* (1985) and Murray *et al.* (1986) and more recently by Berninger *et al.* (1989). Kulikowski *et al.* (1989) showed that red-green isoluminant, low spatial frequency gratings generate a VEP distinctly different from that generated by equivalent luminance modulated gratings. In monkey, phasic (M) cells give similar transient responses to pattern onset, offset and reversal for an equivalent contrast change (Lee *et al.*, 1989*a*). Tonic (P) cells, however, generally have a prominent sustained response which, being linear, is different for stimulus onset and offset (Lee *et al.*, 1989*a*). In humans onset and reversal responses are quite similar for low spatial frequency achromatic stimulation but quite different when chromatic stimuli are used (Kulikowski and Parry, 1987). In the majority of human subjects we have found that these differences are manifest as a negative visual evoked potential (VEP) in response to chromatic onset and a positivity of approximately the same latency in response to achromatic onset or reversal. Furthermore, the spatial and temporal characteristics of the VEP obtained at isoluminance (Murray *et al.*, 1986) correspond to those of the chromatic system as revealed psychophysically (Mullen, 1985).

In this paper we describe the use of isoluminant and luminance modulated gratings and luminance modulated checkerboard stimuli to investigate the chromatic-specific and luminance-specific VEPs obtained from a group of patients with multiple sclerosis or optic neuritis. These electrophysiological measures have been compared with data from the psychophysical procedure of spectral sensitivity which also provides an index of the integrity of chromatic and achromatic pathways. A major objective of the study is to address the issue of selective damage to either chromatic or achromatic mechanisms.

METHODS

Patients

Patients with MS were invited to take part in the study when they were admitted to the Neurology ward at Manchester Royal Infirmary for investigation Informed consent was obtained. Of the 42 patients initially examined, 32 were included in the study. Eight were excluded because they did not complete all of the tests, 1 because of a cataract and 1 due to oscillopsia. Twenty-eight patients exhibited symptoms of overt optic neuritis at some time during their disease although none was having a relapse of visual symptoms at the time of testing. The clinical details of the patients are shown in Table 1. The diagnostic criteria of Poser *et al.* (1983) were applied with clinical and laboratory diagnoses grouped together. Patients were divided into three categories namely: definite MS; probable MS; and optic neuritis.

Normal controls

Evoked potential measurements were conducted on 31 normal volunteers (62 eyes) and monocular spectral sensitivity was obtained on 35 normal individuals. These subjects were age and sex matched with the patient group and none had any history of neurological disease. All subjects had normal colour vision and visual acuity. When required spectacles were worn.

Psychophysics

100-Hue. The Farnsworth-Munsell 100-Hue test was conducted on each eye for the 20 patients indicated in Table 1. The test was conducted under standardized conditions using a Macbeth daylight cabinet.

Spectral sensitivity. A detailed description of the experimental method can be found in King-Smith and Carden (1976). Using a two-channel Maxwellian view system with a 3 mm artificial pupil a 1 deg test spot was presented on a bright (1000 Td) white background (colour temperature 3200 K). Narrow band Balzer B40 interference filters were used to vary the wavelength of the test spot from blue to red in 11 steps (peak wavelengths 402, 423, 450, 474, 497, 527, 554, 574, 601, 622 and 652 nm; average half-height bandwidth 22 nm). The test spot was modulated on-off by a shutter. The method of adjustment was used to determine threshold using at least two readings for each wavelength. For 1 Hz presentation the subject was instructed to reduce the intensity of the test spot until it just disappeared. At 25 Hz presentation rate the instruction was to decrease the intensity until the test spot just stopped flickering. In cases where a fatigue effect was apparent, patients' exposure time to the supra-threshold stimulus was limited by giving frequent rests and high supra-threshold luminances were avoided.

Evoked potentials. The stimuli were generated on a colour television (Ferguson TX) of mean luminance 50 cd/m^2 using a custom-built computer interface. The spatial characteristics of the stimulus, its

TABLE I. DETAILS OF PATIENTS

Initials	*Sex*	*Age (yrs)*	*Diagnosis*	*Duration of disease (yrs)*	*Affected eye*		*Acuity*		*100-Hue test performed?*
					Right	*Left*	*Right*	*Left*	
WK	F	56	DEF	17.0	Y	Y	6/6	6/9	–
CB	M	49	PROB	10.4	–	–	6/5	6/5	Y
HD	F	26	PROB	2.1	–	Y	6/5	6/6	–
MHo	F	37	ON	0.8	Y	–	6/12	6/6	–
LB	F	27	ON	0.1	–	Y	6/5	6/6	–
LF	F	38	DEF	10.6	Y*	Y	6/9	6/6	Y
IW	F	47	PROB	14.0	Y	Y	6/6	6/6	–
VF	F	38	DEF	0 6	–	–	6/5	6/5	–
SC	F	23	DEF	0.3	–	Y	6/6	6/6	–
MHe	M	24	ON	0.5	Y	AMB	6/9	6/18	–
PR	F	48	DEF	0.3	–	Y	6/5	6/6	–
SR	F	22	DEF	1.5	Y*	–	6/9	6/6	Y
CHo	F	26	DEF	2.8	–	Y	6/5	6/5	–
JP	F	48	DEF	13 0	–	Y	6/5	6/5	Y
AK	M	56	ON	1.5	Y	Y	6/5	6/5	–
GW	M	26	DEF	6 3	–	Y	6/5	6/5	–
RV	F	19	PROB	0.2	Y*	–	6/5	6/5	Y
PT	M	43	ON	1.2	–	Y	6/5	6/18	Y
JC	F	27	DEF	1.4	Y	Y	6/5	6/5	Y
GK	M	32	DEF	12.0	Y	Y*	6/18	6/36	Y
AB	M	40	ON	1.3	–	Y*	6/5	6/60	Y
AD	M	24	ON	8.0	Y	–	6/6	6/5	Y
MP	F	34	ON	0.1	Y	Y	6/6	6/6	Y
DS	F	33	ON	2.8	Y	–	6/6	6/6	Y
RW	F	54	DEF	10 0	AMB	–	6/9	6/9	Y
JB	F	25	PROB	5.9	–	–	6/5	6/5	Y
AGa	F	21	PROB	2.8	Y	Y	6/6	6/6	Y
EK	F	47	DEF	3.7	–	–	6/5	6/5	Y
PP	F	28	PROB	7.2	–	–	6/5	6/5	Y
SH	F	39	DEF	11.0	Y	Y*	6/9	6/9	Y
AGo	F	28	DEF	1.8	Y*	–	6/9	6/5	Y
CHa	F	48	DEF	1.4	Y	Y	6/6	6/6	Y

*Clinical details of patients included in the study: DEF = definite MS, PROB = probable MS, ON = optic neuritis, AMB = amblyopic; asterisk indicates that the value of A was less than 2.0 log units.

presentation mode (on-off or pattern reversal) and timing were under the control of a BBC microcomputer. Checkerboard stimuli consisted of 60 min yellow-dark yellow checks of contrast 0.72 which were reversed in phase at 1.85 Hz (260 ms phase 1, 280 ms phase 2). Square-wave grating stimuli were of low contrast (c = 0.11), low spatial frequency (2 c/deg) and were presented on-off at 0.96 Hz (260 ms on, 780 ms off). The stimulus offset had the same mean luminance and mean hue as the pattern. Chromatic red-green isoluminant gratings were produced by superimposing a red grating and a green grating 180 deg out of phase to produce chromatic contrast 0.11 (*see* Murray *et al.*, 1986). For each subject isoluminance was determined using the method of heterochromatic flicker photometry (HFP). That is, the red-green grating was reversed in phase at 12.5 Hz whilst the observer varied the proportions of red and green in the stimulus until a minimum flicker point was found. Five readings were taken for each eye and averaged. In some of the patients the range over which no flicker was detected was very wide so a lower temporal frequency was used to improve precision. Where isoluminance could not be determined for one eye the value for the fellow eye was used. For all stimuli a 'D' shaped field was used which was an 8 deg circle with the top 3 deg covered (*see* inset of Fig. 1). Recordings were made using a four channel Cadwell 7600 averager modified to give a bandpass frequency response of 1–40 Hz. Reproducibility was checked by recording two averages each of 100 sweeps. Sweep duration was 500 ms. Ag/AgCl electrodes were placed at Oz. Reference was linked ears and a forehead electrode acted as an earth. Impedances were maintained below 5 Kohms.

RESULTS

Normal controls

Fig. 1 illustrates evoked potential and psychophysical results for the normal control group. Fig. 1A illustrates the grand averaged VEP waveforms from 10 of the normal subjects (20 eyes). Responses generated by a conventional high contrast pattern reversal checkerboard (*top*), a chromatic grating (*middle*) and an achromatic grating (*bottom*) are illustrated. Notice that the onset of the chromatic grating produces a response which is negative-going at around 130 ms whereas the responses to the achromatic stimuli are predominantly positive at this latency. This effect holds for the majority of normals. Two achromatic VEPs are illustrated: a high contrast reversing checkerboard response which is the method of choice in many clinics and a VEP generated by low contrast, low spatial frequency gratings which, like the checkerboard VEP, is dominated by a strong positivity. Both are dominated by transient-type mechanisms and represent the activity of luminance channels (Kulikowski and Parry, 1987).

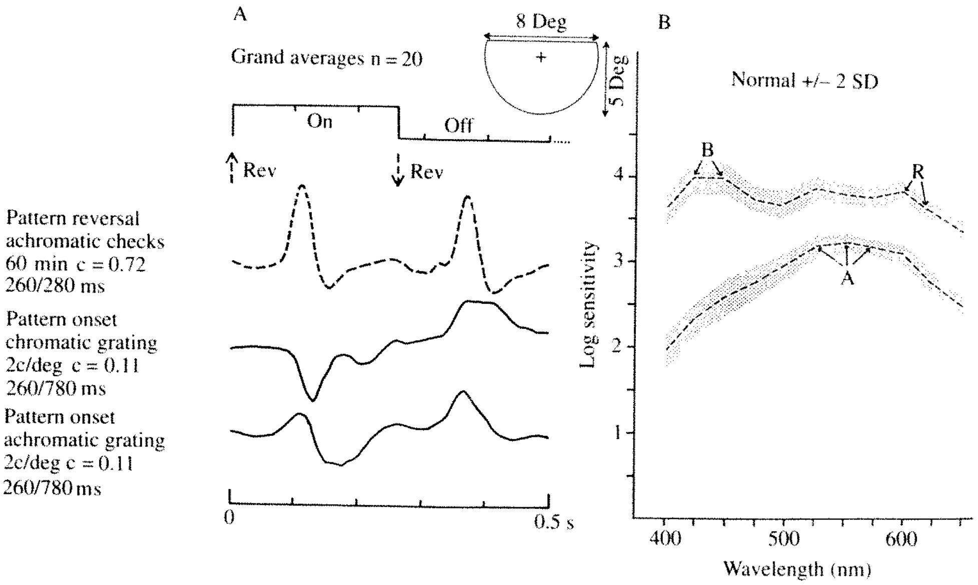

FIG. 1. A, grand average VEPs for 20 normal eyes for the three stimulus conditions used. Upper trace (dashed line) is average response to pattern reversal of 60 min yellow-dark yellow checkerboard, contrast = 0.72. Middle trace is average response to onset-offset presentation of 2 c/deg isoluminant red-green grating where the contrast of the constituent gratings = 0.11. Lower trace is average response to onset-offset presentation of 2 c/deg yellow-dark yellow grating where contrast = 0.11. Inset; illustration of stimulus dimensions, the cross indicates fixation 1 deg down from the upper edge. B, mean spectral sensitivity (log units) at 1 Hz (upper dashed line) and 25 Hz (lower dashed line) for 35 normal eyes. Shaded area indicates plus and minus 2 SDs. Index B is the mean of the 1 Hz spectral sensitivity (log units) at 423 and 450 nm; index R is the mean of the 1 Hz spectral sensitivity (log units) at 601 and 622 nm; index A is the mean of the 25 Hz spectral sensitivity (log units) at 527, 554 and 574 nm.

In Fig. 1B the mean spectral sensitivity, obtained psychophysically, for 35 eyes is shown. The shaded area represents plus and minus 2 standard deviations from the mean.

The upper curve is that obtained at a presentation rate of 1 Hz and the lower curve shows the flicker detection thresholds obtained at 25 Hz. The peaks in the sensitivity function at 450 nm, 545 nm and 610 nm represent the activity of opponent colour mechanisms, which are subserved only by parvocellular neurons in the visual pathway. Analysis of the spectral sensitivity data was simplified by the use of the three indices B, R and A. B is the mean of sensitivities at 1 Hz for 423 and 450 nm, similarly R is the mean sensitivity for 601 and 622 nm. Thus B and R represent chromatic sensitivity in the blue and red regions respectively. A is the mean sensitivity at 527, 554 and 574 nm of the 25 Hz function and is therefore an index of achromatic sensitivity. B, R and A are indicated on the curves in Fig. 1.

Patients

The mean spectral sensitivity at 1 Hz and 25 Hz for all 62 eyes of patients tested is shown in Fig. 2. Data are divided according to whether patients had experienced symptoms of optic neuritis in the eye. The mean data for eyes where no symptoms of optic neuritis had been experienced (26 eyes) were within normal limits for both tests. For eyes with symptoms (38 eyes) 1 Hz spectral sensitivity appears to be uniformly depressed across the whole spectrum suggesting that there is no wavelength selective

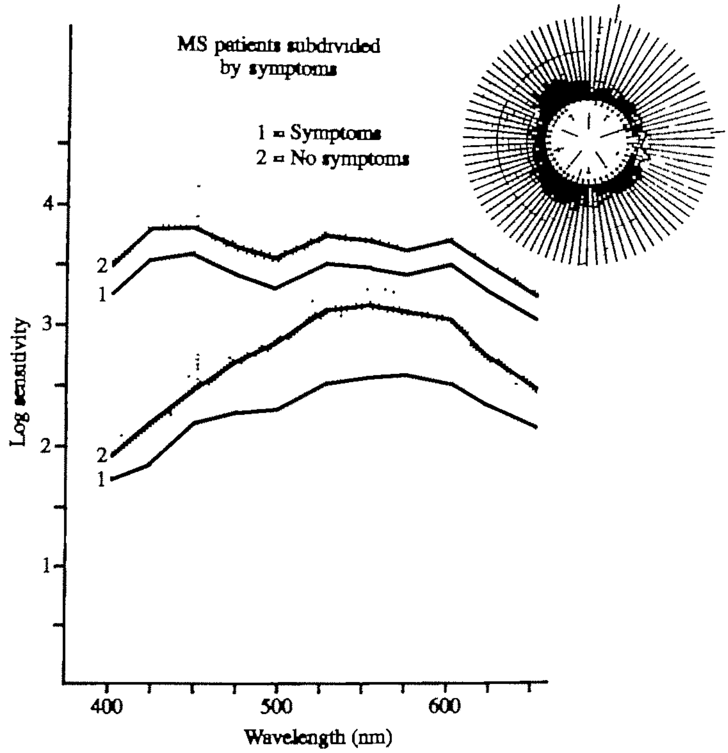

FIG. 2. The mean 1 Hz (*upper*) and 25 Hz (*lower*) spectral sensitivity (log units) for eyes with and without overt symptoms of optic neuritis. Shaded area indicates plus and minus 2 SDs for the normal group. Inset; the mean 100-Hue error scores for 20 patients (40 eyes).

loss. The inset illustrates the average 100-Hue error scores for the patient group. These data show that provided sufficient patients are tested and though individual patients may exhibit short, medium or long wavelength loss, the overall picture is of abnormalities occurring in all regions of the spectrum equally. The Pearson product moment correlation coefficient was calculated between measures of 1 Hz spectral sensitivity and 100-Hue total error scores were highly significant. For short wavelength 1 Hz sensitivity (index B) $r = -0.73$ and $P = 0.0001$, for long wavelengths (index R) $r = -0.79$ and $P = 0.0001$. A plot of 1 Hz spectral sensitivity versus 100-Hue total error score indicated that a 0.5 log unit reduction in sensitivity corresponded to an increase in error score of approximately 300. Comparison of 1 Hz and 25 Hz data for all 62 eyes suggests that marginally greater depression occurs at 25 Hz than at 1 Hz. The 25 Hz data are considered in more detail below.

Whilst it is recognized that there are statistical problems associated with the use of data from both eyes of a subject (Ray and O'Day, 1985) this problem does not arise in this study. The pattern of correlations was hardly affected when only data for right eyes or left eyes were included although there were fluctuations in the values of r and *P*. Fig. 3A,B are scattergrams of B versus R and A versus R. Dots represent sensitivity of non-symptomatic eyes and crosses sensitivity of symptomatic eyes. The plot of B versus R, which indicates the relationship between red and blue defects has a gradient approximately equal to 1 (correlation co-efficient 0.76, $P < 0.0001$) confirming that there is no wavelength specific loss evident in our population of patients. There is, however, a large degree of inter-individual variability exhibited with some patients having marked red or blue defects. Overall, the data highlight the limitations of Köllner's (1912) rule that retinal diseases affect blue-yellow sensitivity and optic nerve diseases cause red-green losses. Fig. 3B demonstrates that there is a more complex relationship between the 1 Hz (in this case represented by R) and 25 Hz spectral sensitivity (A). For most cases there is a linear relationship between A and R showing that losses in achromatic sensitivity are often accompanied by deficits of similar severity in chromatic sensitivity.

The mean 25 Hz spectral sensitivities illustrated in Fig. 2 mask a wide range of abnormality, especially in the symptomatic eyes (*see* Fig. 3B). The mean spectral sensitivity for the 7 eyes with markedly reduced sensitivity ($A < 2.0$ log units) to flicker are shown in Fig. 4B. The mean spectral sensitivity for the remaining 55 eyes is illustrated in Fig. 4A. In Fig. 4B the 1 Hz function (*upper curve*) shows a 0.7 log unit depression with respect to the normal but is parallel to it. These eyes are indicated by an asterisk in Table 1. Five of these have visual acuity 6/9 or better, the remaining 2 have acuities of 6/36 and 6/60. Only symptomatic eyes exhibited such excessively reduced flicker sensitivity. Five out of 7 of these patients were particularly susceptible to adaptation to the flickering stimulus. This fatigue effect meant that the flickering spot appeared to reduce in brightness and then to stop flickering after approximately 1 min of viewing. As indicated in the methods, steps were taken to ensure that this fatigue effect did not distort the overall findings.

Chromatic and achromatic VEPs versus spectral sensitivity

Fig. 5 illustrates the relationship between the amplitude of the chromatic VEP and spectral sensitivity (R) obtained at 1 Hz for symptomatic eyes ($r = 0.31$, $P < 0.02$). The data indicate that for our population of patients chromatic VEP amplitude was reduced

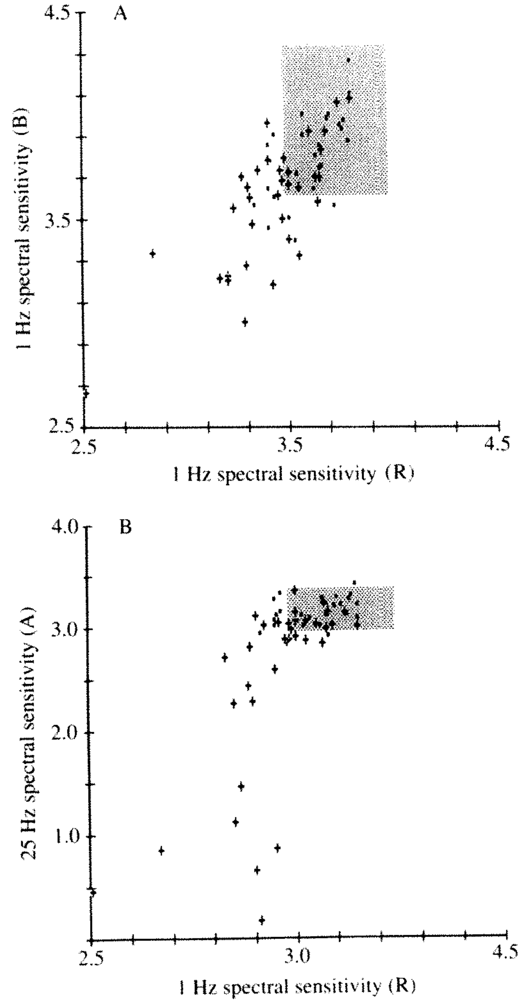

FIG. 3. A, the value of index R (sensitivity at long wavelengths for 1 Hz presentations), plotted against the value of index B (sensitivity at short wavelengths for 1 Hz presentations) for the patient group. Crosses indicate eyes in which there was symptomatic evidence of an episode of optic neuritis. Dots indicate eyes which had no history of visual involvement. The shading indicates the area bound by plus or minus 2 SDs of index R and index B for the normal group of 35 eyes. B, the value of index R (sensitivity at long wavelengths for 25 Hz presentations), plotted against the value of index A (peak sensitivity for 25 Hz presentations) for the patient group. Symbols and shading as for upper panel.

when 1 Hz spectral sensitivity was reduced. This relationship applies to both indices of 1 Hz sensitivity (B and R). Table 2 illustrates the results of statistical analysis of these data, as elsewhere Pearson product moment correlation coefficient (in brackets) and levels of significance are stated. The amplitude of the achromatic VEPs shows no significant correlation with B or R but a weak relationship to 25 Hz spectral sensitivity. Thus the amplitudes of the two types of VEP appear to reflect different aspects of visual dysfunction: the chromatic VEP appears to be an indicator of 1 Hz spectral sensitivity and therefore provides an index of chromatic function; the achromatic VEP shows a weak association with luminance measures.

Table 2 shows the relationships between the psychophysical tests and the latencies and amplitudes of the VEPs. Latencies of both chromatic and achromatic (checkerboard) VEPs show a close relationship with achromatic sensitivity as measured with the 25 Hz flickering target. The amplitude of the chromatic VEP is statistically related to 1 Hz

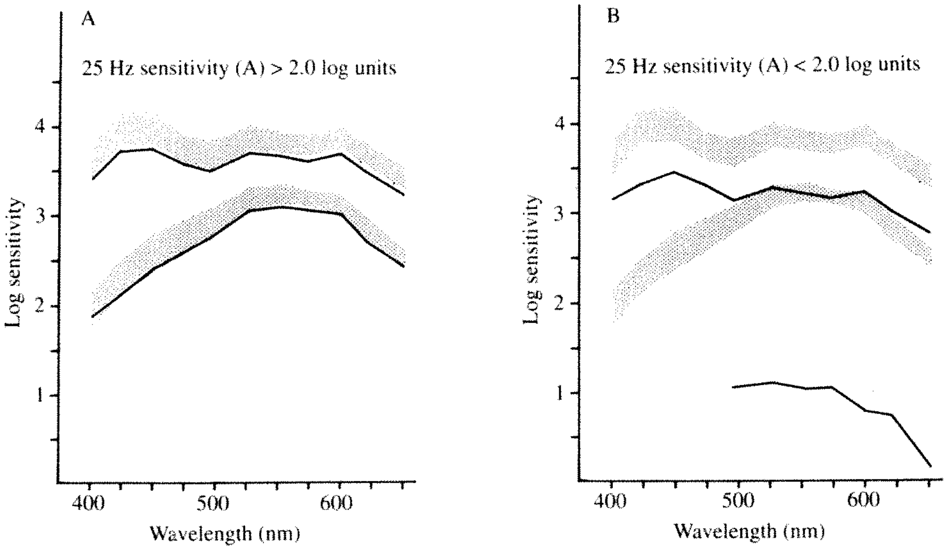

FIG. 4. A, mean 1 Hz (upper line) and 25 Hz (lower line) spectral sensitivity (log units) for eyes of patients where index A (peak 25 Hz spectral sensitivity) is greater than 2.0 log units (55 eyes). B, mean 1 Hz and 25 Hz spectral sensitivity for eyes where index A is less than 2.0 log units. Shaded area indicates range between plus or minus 2 SDs for the normal group (35 eyes).

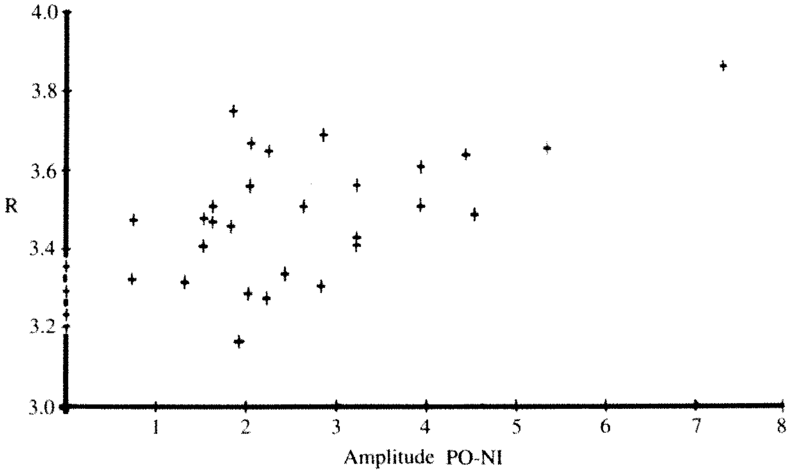

FIG. 5. The amplitude of the chromatic VEP (measured P0−N1) plotted against the value of R (long wavelength 1 Hz spectral sensitivity) for eyes with symptoms of optic neuritis.

spectral sensitivity, but importantly for this study, has no relationship to 25 Hz spectral sensitivity. This illustrates further the selectivity of the chromatic VEP stimulus. As discussed above, this selectivity relies on the use of low contrast stimuli. However, when low contrast achromatic grating stimuli are used the signal to noise ratio is poor.

TABLE 2 CORRELATIONS BETWEEN SPECTRAL SENSITIVITY AND VEP MEASURES

		Spectral sensitivity		
		B	*R*	*A*
VEP-high contrast reversing achromatic checks	N−P100 (amplitude)	NS	NS	NS
	P100−N (amplitude)	NS	NS	0.1 (0.23)
	P100 (latency)	0.1 (−0.24)	0.001 (−0.41)	0.0001 (−0.58)
VEP-low contrast chromatic grating onset	P0−N1 (amplitude)	0.02 (0.33)	0.02 (0.31)	NS
	N1−P1 (amplitude)	0.05 (0.26)	0.05 (0.27)	NS
	N1 (latency)	0.02 (−0.32)	0.002 (−0.40)	0.0001 (−0.61)
VEP-low contrast achromatic grating onset	N0−P1 (amplitude)	NS	NS	0.05 (0.29)
	P1−N1 (amplitude)	NS	NS	NS
	P1 (latency)	NS	NS	NS

Significance values are quoted where this was 0.1 or less and correlation coefficients are given in brackets, NS = not significant, where $P > 0.1$.

As a result there was no significant correlation between the electrophysiology and psychophysics under these conditions. Achromatic VEP amplitudes do show weak correlations with 25 Hz spectral sensitivity but no significant correlation with 1 Hz spectral sensitivity.

DISCUSSION

Chromatic and luminance pathways

One of the main questions addressed in this paper is whether there is any evidence for selective damage to either chromatic or achromatic pathways in demyelinating disease. Overall, the population of patients does not exhibit any evidence for such selective damage. This finding is consistent with Foster *et al.* (1985) but as outlined in the Introduction, other workers who have used different techniques for stimulating chromatic and achromatic mechanisms have reached different conclusions. To some extent these discrepancies may have been due to the use of small populations of patients with different clinical profiles.

In some (7 out of 32) patients there is severe impairment of 25 Hz spectral sensitivity. Abnormalities when high temporal frequencies are employed have been reported previously (e.g. Parsons and Miller, 1957). There are other examples of impairment of processing of high frequency information such as loss of vibration sensitivity and these are almost certainly related to the inability of demyelinated nerve fibres to transmit rapid trains of impulses (McDonald and Sears, 1970). The equivalent finding in the visual pathway, that of reduced flicker sensitivity and temporal resolution, deserves cautious interpretation. Abnormal temporal properties are characteristic of fibres which have suffered loss of myelin, intermittent conduction block and conduction slowing are common. The loss of ability to conduct higher temporal frequencies might appear to be a defect of the fibres which are specialized to carry high temporal frequency information. This is not necessarily the case. A much simpler explanation would be that demyelination does not selectively affect a particular fibre type but that the effects of myelin loss only become manifest at high temporal frequencies.

This point is addressed specifically in the present study by subdividing the patients according to whether they exhibited moderate or extensive (A $<$ 2.0 log units) sensitivity loss at 25 Hz (Fig. 4). The 1 Hz sensitivity of only the (7) patients with extensive loss of 25 Hz sensitivity has then been replotted (Fig. 4B). It is known that the chromatic system is more sensitive at 1 Hz but that the relative sensitivity of the chromatic and achromatic systems varies with wavelength (King-Smith and Carden, 1976). Specifically, the depth of the notch at 580 nm is said to provide an index of the relative activity of the two mechanisms. When stimulus conditions are manipulated to inhibit the luminance system then the notch is deeper (Foster and Snelgar, 1983; Thornton and Pugh, 1983; Snelgar *et al.*, 1987). This means that any change in the relative sensitivity of the two mechanisms would be manifest as a change in shape of the notch. If the notch increases in depth then this would imply an attenuation of luminance mechanisms and if the notch were absent then this would indicate that chromatic mechanisms are affected. There is no change in the shape or depth of the notch in Fig. 4B suggesting that there is equal damage to chromatic and achromatic pathways in this sub-population of patients. This conclusion is consistent with that of Patterson *et al.* (1981) who showed that abnormal temporal properties are not necessarily a consequence of reduced luminance sensitivity.

The fact that there is no change in the shape of the notch in the 1 Hz data is indirect evidence that there are no selective effects of the demylinating lesion. This view has also been expressed by Foster *et al.* (1985), by Mullen and Plant (1986) and also by Travis and Thompson (1989). But the data in Figs 2, 3, 4 also show that there is no evidence for a wavelength specific loss in the patient group. Averaging across eyes the 1 Hz spectral sensitivity function is parallel to, but slightly reduced with respect to normals. The possibility of wavelength selective loss was also tested using the Farnsworth Munsell 100-Hue test. Both techniques allow the investigation of red-green and yellow-blue deficits (unlike Ishihara pseudo-isochromatic plates which are designed for the detection of red-green defects only). Furthermore, the spectral sensitivity technique is based on spectral colours measured at threshold whilst the 100-Hue test uses desaturated colours presented at supra-threshold levels of contrast. Hence these two different but complementary techniques leave little doubt that whilst wavelength selective damage may occur in individuals, there is no systematic wavelength deficit associated with demyelination.

Comparison of VEP and psychophysical findings

Since the pioneering work of Halliday *et al.* (1972) who showed that the pattern reversal VEP is delayed in optic neuritis, the rationale for recording VEPs in patients with demyelinating disease has remained unchanged. The value of the technique lies in its ability to reveal the presence of a clinically silent lesion in the visual pathway in patients in whom signs of demyelination are evident in other parts of the CNS, thus confirming the diagnosis of MS. The use of high contrast checks has practical appeal: it is easy to perform and large responses are obtained because the checkerboard contains a wide spectrum of spatial frequencies at different orientations (Kelly, 1976; De Valois *et al.*, 1979). Usually checkerboard patterns are reversed in phase and Kulikowski and Parry (1987) have shown that this form of presentation is likely to be a strong stimulus to phasic neurons with predominantly transient response characteristics. If large checks are used then the presence of low spatial frequency components will also encourage the activity of transient-type neurons. It follows that, although there may be some functional overlap, large reversing checks will generate a response which is overwhelmingly dominated by magnocellular activity.

It is for these reasons that two forms of achromatic stimulation have been utilized in the present study. A traditional reversing check VEP has been recorded which has similar properties to that obtained from low spatial frequency gratings. The responses to checkerboard stimuli have much better signal/noise characteristics than the low spatial frequency response and this has been used to monitor the activity of magnocellular neurons. To complement this a chromatic (red-green isoluminant) stimulus which activates parvocellular neurons with sustained response characteristics has also been recorded. Although some M cells can respond to isoluminant red-green borders (Lee *et al.*, 1989*a*), these are only significant at higher contrast than that used here (Lee *et al.*, 1989*b*). In addition, Kulikowski *et al.* (1989) and Kulikowski and Russell (1989) showed that even under conditions which favour the activation of phasic units, i.e. pattern reversal at a high temporal rate, the responses were minimal at isoluminance.

Plant (1983) used a wide range of spatial frequencies to stimulate different populations of neurons. He showed that pattern reversal presentation generated a much smaller response at higher spatial frequencies than on-off presentation, and that the VEP delay obtained varied with the type of stimulus used. The use of grating stimuli to improve the selectivity of VEPs enabled Plant and Hess (1986, Fig. 9.1, p. 198) to show that whilst amplitude reduction is correlated with changes in contrast sensitivity this shows only a tenuous relationship to abnormalities in VEP latency. In the present study, stimuli which increase the functional selectivity of VEPs have been used to separate chromatic and achromatic mechanisms.

Comparisons between the psychophysical and evoked potential measures are made by calculating Pearson product moment correlations. In some cases there are compelling *a priori* reasons for expecting a statistically significant relationship to emerge. For example, both 1 Hz spectral sensitivity and chromatic VEPs can be regarded as measures of activity of chromatic channels and a correlation between the two might therefore be expected. The data in Table 2 show that, despite the different stimulus conditions used, this is indeed the case. A decrease in sensitivity at 1 Hz is accompanied by reduced amplitude of the chromatic VEP. The implication of this observation is that both of these techniques provide evidence for damage to fibres carrying chromatic information.

Equally important is the observation (Table 2) that chromatic VEP amplitude is not correlated with flicker detection as determined by psychophysically obtained, 25 Hz spectral sensitivity. This is further evidence for some degree of selectivity in the VEP stimuli used in these experiments. If both VEP and psychophysical stimuli were perfectly selective for chromatic and achromatic mechanisms then there would be a very strong association between the chromatic VEP amplitude and 1 Hz spectral sensitivity and the achromatic VEP amplitude and 25 Hz spectral sensitivity. In our data there exists a weak relationship between achromatic VEP and 25 Hz spectral sensitivity but it is important to recognize that there is no evidence of an association between achromatic VEP amplitude and 1 Hz spectral sensitivity.

The latency of the VEP is less variable than amplitude and statistically significant trends in patient data are therefore more readily detected using latency than amplitude measures. However, apart from the inter-individual variability in amplitude some co-variation between amplitude and latency is inevitable because jitter in the visual signal as it reaches the visual cortex will result in a delay and a reduction in amplitude because of the spread in the waveform. Table 2 indicates that a strong relationship between flicker detection and the latency of both the achromatic chromatic VEP exists. Similar findings were reported by Wright *et al.* (1987) using achromatic stimuli. It appears that latency changes, in both chromatic and achromatic VEPs, are indicative of abnormalities in the temporal frequency characteristics of the visual pathway. The physiological consequences of demyelination, that is, conduction slowing, intermittent blockage and prolonged refractory period may all contribute to differing extents to these abnormalities.

It is difficult, but just possible, to account for the large inter-ocular VEP latency differences seen in optic neuritis simply on the basis of conduction slowing in the first 5 cm (pre-chiasmal section) of the visual pathway (McDonald, 1977; Ikeda *et al.*, 1978). Very low conduction velocities would be required for the mean increase in latency seen in optic neuritis to occur. It seems likely that impairment in the ability of pre-cortical neurons to conduct high temporal frequencies contributes in some way to the delay and the data presented in this paper support this proposition. In macaques, retinal ganglion cells and LGN cells respond at very high temporal frequencies but strong attenuation of these signals occurs in the visual cortex (Crooke *et al.*, 1988) and the consequent long integration times leads to a delay in the time-to-peak of gross potentials (Cruetzfeldt *et al.*, 1969). Temporal distortion of the pre-cortical signal in the form of selective loss of high temporal frequencies might therefore be expected to be manifest as a further delay.

In summary, although high temporal frequency sensitivity is substantially impaired in a proportion of MS patients we have argued that this is not necessarily evidence for selective damage to thick fibres. In addition, whilst individual patients may exhibit a blue or red colour defect, there is no evidence that the one is more common than the other in our patient group. Finally, the amplitude of the chromatic VEP recorded in these experiments shows a statistically significant correlation with psychophysical measures of the sensitivity of chromatic mechanisms but no correlation with that of achromatic mechanisms. We suggest that chromatic VEPs will prove to be an informative tool for the investigation and monitoring of the visual pathology associated with MS and in other conditions in which colour vision deficiencies are evident.

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REFERENCES

Alvarez SL, King-Smith PE, Bhargava SK (1982) Luminance and colour dysfunction in retrobulbar neuritis. *Documenta Ophthalmolologica Proceedings Series*, **33**, 441–443.

Berninger TA, Arden GB, Hogg CR, Frumkes T (1989) Separable evoked retinal and cortical potentials from each major visual pathway: preliminary results. *British Journal of Ophthalmology*, **73**, 502–511.

Carden D, Kulikowski JJ, Murray IJ, Parry NRA (1985) Human occipital potentials evoked by the onset of equiluminant chromatic gratings. *Journal of Physiology, London*, **369**, 44*P*.

Creutzfeldt O, Rosina A, Ito M, Probst W (1969) Visual evoked response of single cells and of the EEG in primary visual area of the cat. *Journal of Neurophysiology*, **32**, 127–139.

Crook JM, Lange-Malecki B, Lee BB, Valberg A (1988) Visual resolution of macaque retinal ganglion cells. *Journal of Physiology, London*, **396**, 205–224.

De Monasterio FM, Gouras P (1975) Functional properties of ganglion cells of the rhesus monkey retina. *Journal of Physiology, London*, **251**, 167–195.

De Valois KK, De Valois RL, Yund EW (1979) Responses of striate cortex cells to grating and checkerboard patterns. *Journal of Physiology, London*, **291**, 483–505.

Dreher B, Fukada Y, Rodieck RW (1976) Identification, classification and anatomical segregation of cells with X-like and Y-like properties in the lateral geniculate nucleus of old-world primates. *Journal of Physiology, London*, **258**, 433–452.

Fallowfield L, Krauskopf J (1984) Selective loss of chromatic sensitivity in demyelinating disease. *Investigative Ophthalmology and Visual Science*, **25**, 771–773.

Foster DH, Snelgar RS (1983) Test and field spectral sensitivities of colour mechanisms obtained on small white backgrounds: action of unitary opponent-colour processes? *Vision Research*, **23**, 787–797.

Foster DH, Snelgar RS, Heron JR (1985) Nonselective losses in foveal chromatic and luminance sensitivity in multiple sclerosis. *Investigative Ophthalmology and Visual Science*, **26**, 1431–1441.

Gouras P (1968) Identification of cone mechanisms in monkey ganglion cells. *Journal of Physiology, London*, **199**, 533–547.

Griffin JF, Wray SH (1978) Acquired color vision defects in retrobulbar neuritis. *American Journal of Ophthalmology*, **86**, 193–201.

Halliday AM, McDonald WI, Mushin J (1972) Delayed visual evoked response in optic neuritis. *Lancet*, **i**, 982–985.

Halliday AM, McDonald WI (1977) Pathophysiology of demyelinating disease. *British Medical Bulletin* **33**, 21–27.

Heron JR, Regan D, Milner BA (1974) Delay in visual perception in unilateral optic atrophy after retrobulbar neuritis. *Brain*, **97**, 69–78

Hicks TP, Lee BB, Vidyasagar TR (1983) The responses of cells in macaque lateral geniculate nucleus to sinusoidal gratings. *Journal of Physiology, London*, **337**, 183–200.

Hubel DH, Wiesel TN (1972) Laminar and columnar distribution of geniculo-cortical fibers in the macaque monkey. *Journal of Comparative Neurology*, **146**, 421–450.

Ikeda H, Tremain KE, Sanders MD (1978) Neurophysiological investigation in optic nerve disease: combined assessment of the visual evoked response and electroretinogram. *British Journal of Ophthalmology*, **62**, 227–239.

Ikeda H, Tansey EM (1986) Virus-induced demyelination in the optic nerve of the mouse. I: Morphological and axonal transport studies. In: *Optic Neuritis*. Edited by R. F. Hess and G. T. Plant. Cambridge: Cambridge University Press, pp. 255–270.

Kaplan E, Shapley RM (1982) X and Y cells in the lateral geniculate nucleus of macaque monkeys. *Journal of Physiology, London*, **330**, 125–143.

Kelly DH (1976) Pattern detection and the two-dimensional Fourier transform: flickering checkerboards and chromatic mechanisms. *Vision Research*, **16**, 277–287.

King-Smith PE, Carden D (1976) Luminance and opponent-color contributions to visual detection and adaptation and to temporal and spatial integration. *Journal of the Optical Society of America*, **66**, 709–717.

Köllner H (1912) *Die Störungen des Farbensinnes: Ihre Klinische Bedeutung und Ihre Diagnose*. Berlin: Karger.

KULIKOWSKI JJ, PARRY, NRA (1987) Human occipital potentials evoked by achromatic or chromatic checkerboards and gratings. *Journal of Physiology, London*, **388,** 45*P*.

KULIKOWSKI JJ, RUSSELL MHA (1989) Electroretinograms and visual evoked potentials elicited by chromatic and achromatic gratings. In: *Seeing Contour and Colour.* Edited by J. J. Kulikowski, C. M. Dickinson and I. J. Murray. Oxford: Pergamon Press, pp. 467–470.

KULIKOWSKI JJ, MURRAY IJ, PARRY NRA (1989) Electrophysiological correlates of chromatic opponent and achromatic stimulation in man. In: *Colour Vision Deficiencies IX.* Edited by B. Drum and G. Verriest. Dordrecht: Kluwer Academic, pp. 145–153.

LEE BB, MARTIN PR (1989) Chromatic and luminance channels in the primate visual pathway. In: *Seeing Contour and Colour.* Edited by J. J. Kulikowski, C. M. Dickinson and I. J. Murray. Oxford: Pergamon Press, pp. 21–35.

LEE BB, MARTIN PR, VALBERG A (1989*a*) Nonlinear summation of M- and L-cone inputs to phasic retinal ganglion cells of the macaque. *Journal of Neuroscience,* **9,** 1433–1442.

LEE BB, MARTIN PR, VALBERG A (1989*b*) Sensitivity of macaque retinal ganglion cells to chromatic and luminance flicker. *Journal of Physiology, London,* **414,** 223–243.

LEVENTHAL AG, RODIECK RW, DREHER B (1981) Retinal ganglion cell classes in the Old World monkey: morphology and central projections. *Science,* **213,** 1139–1142.

LIVINGSTONE MS, HUBEL DH (1987) Psychophysical evidence for separate channels for the perception of form, color, movement, and depth. *Journal of Neuroscience,* **7,** 3416–3468.

MCDONALD WI (1977) Pathophysiology of conduction in central nerve fibres. In: *Visual Evoked Potentials in Man: New Developments.* Edited by J. E. Desmedt. Oxford: Clarendon Press, pp. 427–437.

MCDONALD WI (1983) Doyne lecture. The significance of optic neuritis. *Transactions of the Ophthalmological Society of the United Kingdom,* **103,** 230–246.

MCDONALD WI (1986) The pathophysiology of multiple sclerosis. In: *Multiple Sclerosis.* Edited by W. I. McDonald and D. H. Silberberg. London: Butterworths, pp. 112–133.

MCDONALD WI, SEARS TA (1970) The effects of experimental demyelination on conduction in the central nervous system. *Brain,* **93,** 583–598.

MCDONALD WI, SILBERBERG DH (1986) The diagnosis of multiple sclerosis. In: *Multiple Sclerosis.* Edited by W. I. McDonald and D. H. Silberberg. London: Butterworths, pp. 1–10.

MULLEN KT (1985) The contrast sensitivity of human colour vision to red-green and blue-yellow chromatic gratings. *Journal of Physiology, London,* **359,** 381–400.

MULLEN KT, PLANT GT (1986) Colour and luminance vision in human optic neuritis. *Brain,* **109,** 1–13.

MURRAY IJ, PARRY NRA, CARDEN D, KULIKOWSKI JJ (1986) Human visual evoked potentials to chromatic and achromatic gratings. *Clinical Vision Sciences,* **1,** 231–244.

PARSONS OA, MILLER PN (1957) Flicker fusion thresholds in multiple sclerosis. *Archives of Neurology and Psychiatry, Chicago,* **77,** 134–139.

PATTERSON VH, FOSTER DH, HERON JR, MASON RJ (1981) Multiple sclerosis: luminance threshold and measurements of temporal characteristics of vision. *Archives of Neurology, Chicago,* **38,** 687–689.

PLANT GT (1983) Transient visually evoked potentials to sinusoidal gratings in optic neuritis. *Journal of Neurology, Neurosurgery and Psychiatry,* **46,** 1125–1133.

PLANT GT, HESS RF (1986) The electrophysiological assessment of optic neuritis. In: *Optic Neuritis.* Edited by R. F. Hess and G. T. Plant. Cambridge: Cambridge University Press, pp. 192–229.

POSER CM, PATY DW, SCHEINBERG L, MCDONALD WI, DAVIS FA, EBERS GC *et al.* (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology,* **13,** 227–231.

RAY WA, O'DAY DM (1985) Statistical analysis of multi-eye data in ophthalmic research. *Investigative Ophthalmology and Visual Science,* **26,** 1186–1188.

REGAN D, RAYMOND J, GINSBURG AP, MURRAY TJ (1981) Contrast sensitivity, visual acuity and the discrimination of Snellen letters in multiple sclerosis. *Brain,* **104,** 333–350.

SHIBASAKI H, MCDONALD WI, KUROIWA Y (1981) Racial modification of clinical picture of multiple sclerosis: comparison between British and Japanese patients. *Journal of the Neurological Sciences,* **49,** 253–271.

SNELGAR RS, FOSTER DH, SCASE MO (1987) Isolation of opponent-colour mechanisms at increment threshold. *Vision Research,* **27,** 1017–1027.

SPERLING HG, HARWERTH RS (1971) Red-green cone interactions in the incremental-threshold spectral sensitivity of primates. *Science,* **172,** 180–184.

THORNTON JE, PUGH EN (1983) Red/green color opponency at detection threshold. *Science*, **219**, 191–193.

TOOTELL RBH, SILVERMAN MS, HAMILTON SL, DE VALOIS RL, SWITKES E (1988) Functional anatomy of macaque striate cortex. III. Color. *Journal of Neuroscience*, **8**, 1569–1593.

TRAVIS D, THOMPSON P (1989) Spatiotemporal contrast sensitivity and colour vision in multiple sclerosis. *Brain*, **112**, 283–303.

WIESEL TN, HUBEL DH (1966) Spatial and chromatic interactions in the lateral geniculate body of the rhesus monkey. *Journal of Neurophysiology*, **29**, 1115–1156.

WRIGHT CE, DRASDO N, HARDING GFA (1987) Pathology of the optic nerve and visual association areas. *Brain*, **110**, 107–120.

WYSZECKI G, STILES WS (1967) *Color Science: Concepts and Methods, Quantitative Data and Formulas*. New York: John Wiley.

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Brain (1991), **114**, 2437–2450

THE PATHOPHYSIOLOGY OF ACUTE OPTIC NEURITIS

AN ASSOCIATION OF GADOLINIUM LEAKAGE WITH CLINICAL AND ELECTROPHYSIOLOGICAL DEFICITS

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SUMMARY

Eighteen patients with acute optic neuritis underwent optic nerve magnetic resonance imaging (MRI) before and after injection of gadolinium-diethylene triamine pentacetic acid (Gd-DTPA). Ten were re-examined 4 wks later. Leakage of Gd-DTPA across the blood-optic nerve barrier was a consistent finding in the acute lesion, and its presence was associated with abnormal visual acuity and colour vision, retro-ocular pain on eye movement, an afferent pupillary defect, and a reduced amplitude of the P100 component of the visual evoked potential. Gd-DTPA leakage had ceased in 9/11 nerves when restudied 4 wks later, and this evolution was associated with improved visual acuity and an increased P100 amplitude. Leakage is likely to reflect inflammation, and we conclude that the latter plays an important part in the production of conduction block and clinical deficit, and that its resolution is an important step in clinical remission from acute episodes of demyelination.

INTRODUCTION

In the early stages of multiple sclerosis (MS), the clinical pattern is characteristically one of relapse and remission. The pathophysiological mechanisms underlying this sequence of events are poorly understood because, until recently, there has not been a satisfactory means of characterizing *in vivo* the evolving pathological process. An improved understanding of such mechanisms is desirable as it may lead to new therapeutic strategies.

To some extent, magnetic resonance imaging (MRI) allows the observation of pathology *in vivo*. MRI in most MS patients shows a pattern of multifocal white matter cerebral lesions (Young *et al.*, 1981; Lukes *et al.*, 1983; Runge *et al.*, 1984), with a similar distribution to demyelinated plaques seen pathologically. That the lesions are indeed plaques is supported by post-mortem MRI/pathological correlations (Stewart *et al.*, 1984; Ormerod *et al.*, 1987). *In vivo* studies have shown that leakage of Gd-DTPA across an abnormal blood-brain barrier is a feature in some brain lesions (Grossman *et al.*, 1986), especially new ones (Miller *et al.*, 1988*a*; Bastianello *et al.*, 1990; Harris *et al.*,

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1991; Thompson *et al.*, 1991). In chronic relapsing experimental allergic encephalomyelitis, Gd-DTPA-enhancement correlates with inflammation (Hawkins *et al.*, 1990). Given the clinical and pathological similarities of this experimental disease and MS (Lassman, 1983), the correspondence between the pattern of enhancement and the known pattern of inflammation at post-mortem (Prineas and Connell, 1979), and the recent histological confirmation of inflammation a few days after a lesion had been shown to enhance (Katz *et al.*, 1990), it is probable that Gd-DTPA-enhancement represents inflammation in the human disease too.

Thus, it should be possible to ascertain, through a correlative MRI/clinical study, the relationship of a pathological feature (inflammation) to the clinical deficit in an acute demyelinating lesion. Most lesions in the brain are unsuitable for such a study as they are asymptomatic (Ormerod *et al.*, 1987; Paty *et al.*, 1988; Thompson *et al.*, 1990). In contrast, lesions in the optic nerve are particularly suitable because of their characteristic clinical presentation, acute optic neuritis. With the use of an MRI sequence which suppresses the signal from orbital fat, it is possible to identify the symptomatic lesion in patients with optic neuritis (Miller *et al.*, 1988*b*). There is also an opportunity to assess conduction through the lesion by using visual evoked potentials (VEPs). We therefore performed a correlative clinical/MRI/VEP study of a group of patients with acute optic neuritis.

METHODS

Patients

Eighteen adult patients, aged 18–48 yrs with clinically isolated acute optic neuritis were recruited from Moorfields Eye Hospital (we limited recruitment to those with isolated optic neuritis, since they are also enrolled in a separate, ongoing prospective study of the prognostic significance of brain MRI at presentation for subsequent progression to multiple sclerosis). Informed consent for the examinations was obtained from all patients. There were 11 females and 7 males. Diagnosis was based on standard clinical criteria (Compston *et al.*, 1978) and in each case was supported by the presence of an abnormal VEP. None of the patients was treated with corticosteroids during the study period.

Summary of investigations

Ten patients (9 unilateral optic neuritis, 1 bilateral simultaneous optic neuritis) had MRI on 2 occasions. The first MRI was performed 2–13 d (mean 6.4) after the onset of blurring of vision at which time both neuro-ophthalmological and VEP examinations were obtained in all 10 patients. Follow-up MRI was performed 20–32 d (mean 27.8) later at which time neuro-ophthalmological examination was repeated in all 10 patients, while VEPs were obtained in 9.

Eight patients (7 unilateral optic neuritis, 1 bilateral simultaneous optic neuritis) had a single MRI examination, 8–38 d after the onset of blurring of vision; neuro-ophthalmological and VEP examinations were performed on the same day only in the patient with bilateral simultaneous optic neuritis.

Overall, 20 clinically affected nerves were studied with MRI on a total of 31 occasions. The duration of visual symptoms (to the nearest day) was known for each occasion. Neuro-ophthalmological and VEP examinations were performed on the same day as MRI in 24 and 23 instances, respectively.

Neuro-ophthalmological examination

Patients were first seen by an ophthalmologist to exclude retinal or other intra-ocular pathology. They were then seen by a neurologist (B.D.Y.) who excluded previous significant neurological symptoms and abnormality on general neurological examination. Distance vision was recorded from Snellen charts and near vision was recorded using The Faculty of Ophthalmologists reading test type. Colour vision was assessed with Ishihara plates, the number of errors being recorded on viewing 13 plates. Visual fields were tested to confrontation, and plotted using both a Goldmann perimeter (static and dynamic isopters to I2 and I4 targets) and a Bjerrum screen, and classed as normal or abnormal.

Magnetic resonance imaging

MRI was performed on a Picker 0.5T superconducting imager. The optic nerves were imaged using a STIR sequence ($SE_{2000/40/150}$) to suppress the signal from orbital fat. A binocular orbital surface coil was provided by the manufacturer. 5 mm contiguous coronal slices through the orbits from the head of the optic nerve to the optic chiasm were obtained, before and after the injection of Gd-DTPA 0.2 mmol/kg (Schering AG) (Youl *et al.*, 1991). All scans were independently reported by two neuroradiologists (B.E.K. and I.F.M.) who were unaware of the clinical details. Prior to contrast administration, lesions were defined as foci of increased signal within the nerve. The same 'window' and 'level' were used for the images obtained immediately before and after each injection of Gd-DTPA.

Unlike conventional T_1-weighted spin echo sequences, in which the accumulation of Gd-DTPA in regions with an abnormal blood-brain barrier results in a focal *increase* in signal (i.e. enhancement), there is a *decrease* in signal in such regions on the STIR sequence (Youl *et al.*, 1991). Thus, following contrast administration, Gd-DTPA leakage across an abnormal blood-optic nerve barrier was said to be present when the neuroradiologist determined that there was a definite *reduction* of signal in the previously identified lesion. Because of this 'negative' contrast effect, we refer to such regions as areas of Gd-DTPA 'leakage' rather than 'enhancement' (Fig. 1).

MRI lesions in MS (and by inference in optic neuritis) may vary markedly in their degree of signal abnormality, due to substantial variations in their water proton density and T_1 and T_2 relaxation times (Ormerod *et al.*, 1987). A lesion seen on a single 5 mm slice could therefore have an actual length which is considerably shorter or longer. If the lesion has very long relaxation times, as occurs with vasogenic oedema (Barnes *et al.*, 1986), it might be visible when only 1–2 mm in length; if it exhibits only minor elevations in relaxation times compared with normal white matter, as may be seen in inflammation without oedema (Noseworthy *et al.*, 1988), it could extend several millimeters on to the neighbouring slices without producing signal change. We did not, therefore, consider the current resolution (5 mm thick slices) sufficient

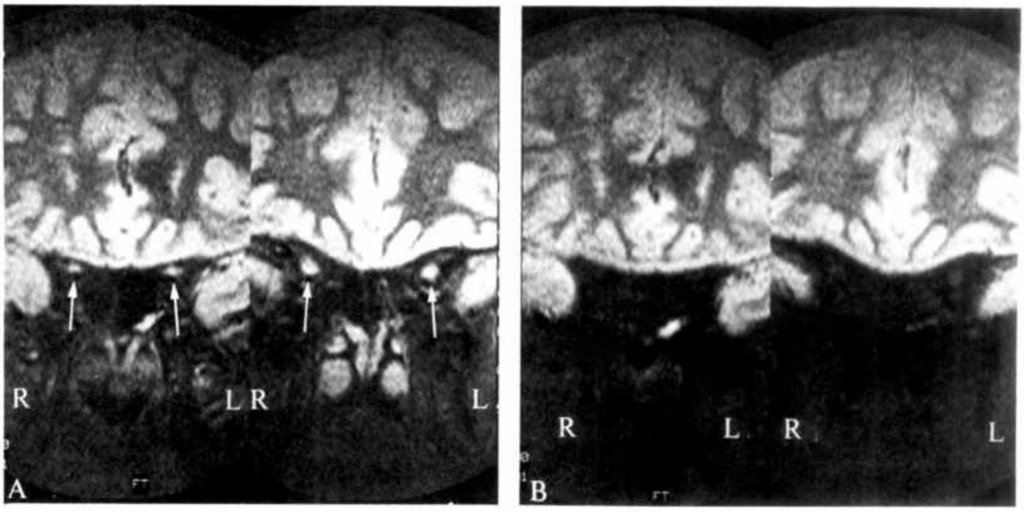

FIG. 1. MR examination ($IR_{2000/40/150}$) from an 18-yr-old male presenting with an 8 day history of bilateral central visual loss. A, pre-contrast scan reveals increased signal in both optic nerves (arrows); B, following Gd-DTPA, there has been a marked fall in signal from the affected segments, indicating 'enhancement' for this scanning sequence (Youl *et al.*, 1991). Signal is also lost from the relatively hyperaemic nasal mucosa, a normal finding.

to allow a precise measurement of the lesion length in millimeters. Thus, in correlating the VEP latency and amplitude with lesion length, the latter was recorded as the number of consecutive 5 mm slices on which it was visible.

Visual evoked potentials

VEPs were recorded monocularly to full field pattern reversal stimulation (GT/ADT). The stimulus was provided by a circular screen whose radius subtended an angle of 16° on to which a checkerboard slide of 50′ black and white squares was back-projected. Pattern reversal was produced every 505 ms by rapid (10 ms) horizontal displacement of the pattern through one square width. The luminance of the white squares was 230 cd/m^2 and the contrast was 98%. The patient was seated with the eye 1 m away from the fixation point, which was a red spot laser in the centre of the screen. Eight trans-occipital recording electrodes were arranged in a standard montage. This included a horizontal array of 5 electrodes placed on a line 5 cm above the inion, one of which was in the midline, with 2 electrodes on either side at an inter-electrode distance of 5 cm. Additional electrodes were placed 2.5 cm above the inion, at the inion and 5 cm below it. The reference electrode was located 12 cm above the nasion.

Two hundred responses were averaged in each run. The amplifier's high frequency response was less than 3 dB down at 5 kHz and the time constant was 1 s. The average sampling interval was 1.25 ms and the averaging window 320 ms. Normal limits were obtained separately from 2 groups of healthy individuals within roughly the same mean age as the patients: 39 females aged 18–38 yrs (mean 23.9 yrs) and 24 males aged 18–39 yrs (mean 25.4 yrs). The normal latency limits of the P100 component were defined by the mean ±2.5 SD of the absolute latency and inter-ocular latency difference. The normal amplitude limits were defined by the mean ±2.5 SD of log amplitude and log (left eye/right eye) amplitude ratio.

RESULTS

MRI-clinical correlations

First MRI. Clinical neuro-ophthalmological assessment was performed on the same day as the first MRI in 11 patients, 2 with bilateral simultaneous and 9 with unilateral optic neuritis. Gd-DTPA leakage was observed in all 13 symptomatic nerves. Compared with the 9 asymptomatic nerves, the 13 symptomatic nerves were significantly associated with reduced distance and near visual acuity, impaired colour vision, visual field abnormality, an afferent pupillary defect, pain on eye movement and swelling of the optic disc ($P = 0.001$ for each clinical feature; Fisher exact probability test).

Visual acuity was worse than 6/9 in 4/6 studies displaying intracanalicular leakage and in 4/7 studies where leakage was confined to the orbital portion of the nerve ($P = 0.25$; χ^2 with Yates' adjustment). Visual acuity was worse than 6/9 in 4/5 studies in which there was Gd-DTPA leakage on 3 or more consecutive 5 mm slices, and in 4/8 studies which displayed leakage on 1 or 2 slices only ($P = 0.1$).

Follow-up MRI. Neuro-ophthalmological assessment was performed on the same day as the follow-up MRI in 10 patients, 1 with bilateral simultaneous and 9 with unilateral optic neuritis. Gd-DTPA leakage was observed in only 2/11 symptomatic nerves. All 11 symptomatic eyes had recovered to a visual acuity of 6/9 or better. Compared with the 9 asymptomatic nerves, the 9 symptomatic nerves which did *not* display Gd-DTPA leakage at follow-up were not significantly associated with reduced distance, near or colour vision, or with pain on eye movement, although they were associated with an abnormal visual field ($P = 0.04$), an afferent pupillary defect ($P = 0.04$) and optic disc swelling ($P = 0.001$) (Fisher's exact probability test).

Lesions showing Gd-DTPA leakage at first MRI and not at follow-up (Table 1). At the time of the first scan there was a significantly higher frequency of abnormal distance,

TABLE 1. CLINICAL FINDINGS IN THOSE LESIONS WHICH 'LEAKED' AT FIRST STUDY BUT NOT AT FOLLOW-UP

	First scan (leaking) (n = 9)	*Follow-up (no longer leaking) (n = 9)*	
Distance acuity <6/5	8	3	$P = 0.04$
Near acuity <N5	8	2	$P = 0.03$
Abnormal colour vision	7	2	$P = 0.04$
Afferent pupillary deficit	9	4	$P = 0.04$
Pain	8	2	$P = 0.03$
Abnormal visual field	7	4	NS
Disc swelling	7	7	NS

(Fisher exact probability test.)

near and colour acuity, pain on eye movement and afferent pupillary defect (Fisher exact probability test.

Correlation of Gd-DTPA leakage with time from onset of symptoms. Of the 31 MRI examinations, Gd-DTPA leakage within the lesion was seen on 18 occasions, for which the time from onset of blurred vision varied between 2 and 37 d (mean 11.8 d). The time from onset in the 13 studies where no Gd-DTPA leakage was apparent varied between 12 and 41 d (mean 31.2 d). These times were significantly different ($P < 0.001$; 2-tailed Student's t test). Gd-DTPA leakage was seen in 6/6 lesions where the time from onset of blurred vision was less than 7 d, in 7/8 lesions where the time from onset was 7–13 d but in only 5/17 lesions where the interval was at least a fortnight (Figs 1–3).

MRI-VEP correlations

First MRI. VEPs were recorded at the time of first MRI in 11 patients, 2 with bilateral simultaneous and 9 with unilateral optic neuritis (Table 2). The VEPs were abnormal for all 13 symptomatic eyes, being absent in 3 eyes, and of increased latency in 9 eyes, in 6 of which there was also a reduced amplitude. In one eye, the VEP was of normal latency but reduced amplitude. In the 10 symptomatic nerves from which a VEP response was obtained (all of which displayed Gd-DTPA leakage) the mean amplitude of the P100 was reduced to about one-third of that in the 9 asymptomatic nerves ($P < 0.001$; t test), and the mean latency was increased by 23 ms ($P < 0.001$; t test).

Follow-up MRI. VEPs were recorded at follow-up in 9 patients (Table 2), 1 with bilateral and 8 with unilateral optic neuritis. Abnormal responses were found in 8 out of 10 symptomatic eyes, with an increased latency in all 8, but a reduced amplitude in only 2. In the 9 symptomatic nerves which no longer displayed Gd-DTPA leakage, the mean amplitude of the P100 was reduced to about half that recorded in the 9 asymptomatic nerves ($P = 0.008$; t test), and the mean latency was increased by 20 ms ($P < 0.001$; t test).

Lesions showing Gd-DTPA leakage at first MRI but not at follow-up. Table 3 and Fig. 4 compare the VEP findings at first scan and follow-up for the 8 eyes whose optic nerve lesion showed this MRI evolution. There was no significant latency difference between the recordings, but the amplitude was significantly larger at follow-up than at the first recording ($P = 0.02$; paired t test).

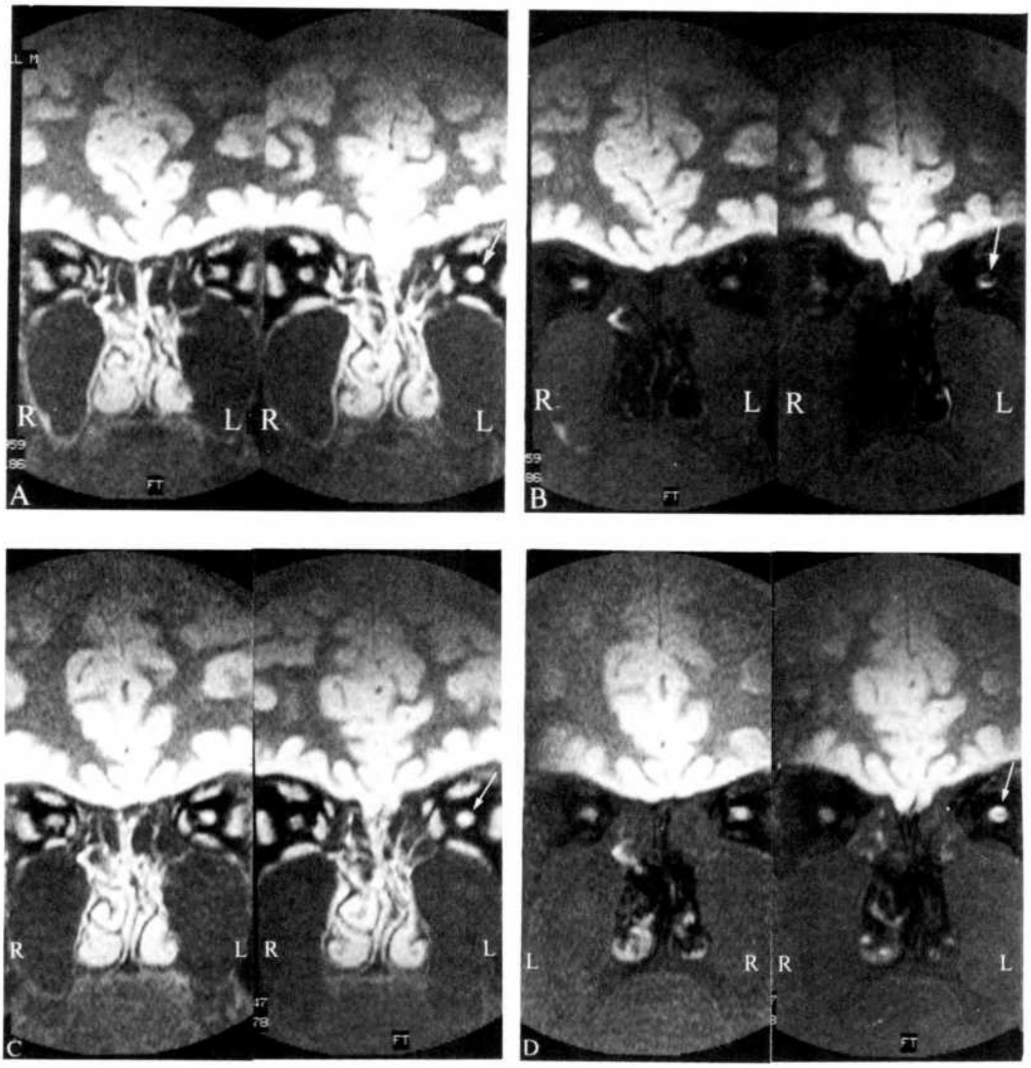

FIG. 2. Series $IR_{2000/40/150}$ scans from a 29-yr-old female (*Case 9*) with left ON. A, first pre-contrast scan (symptoms present for 6 d) reveals increased signal in the left optic nerve (arrowed). B, first scan following injection of Gd-DTPA shows signal decrement in the lesion (arrowed). C, follow-up pre-contrast scan (1 mth later) reveals a persisting high signal lesion (arrowed). D, follow-up scan following injection of Gd-DTPA no longer shows signal decrement in the lesion (arrowed).

Correlation of MRI lesion length with VEP amplitude and latency. We compared P100 latency and amplitude with the length of the pre- and post-contrast MRI lesion both at first MRI and at follow-up. Only one significant correlation was observed: at follow-up, VEP amplitude was inversely correlated with the length of the lesion on the pre-contrast sequence, with a correlation coefficient of -0.84 ($P < 0.01$) and a slope of -1.92 μV/5 mm slice (SEM 0.50) (Fig. 5). The effect accounted for 71% of the variance.

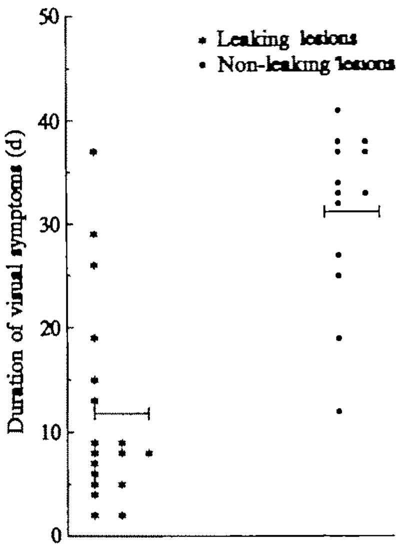

FIG. 3. Optic neuritis: relationship between duration of visual symptoms and presence of Gd-DTPA leakage in the optic nerve.

The regression line intercepted the ordinate at a value of 14.8 μV which is close to the mean amplitude for the asymptomatic eyes (14.1 μV) recorded on the same occasion.

DISCUSSION

There are two main findings in this study. First, the presence of Gd-DTPA leakage was a consistent feature of the early optic nerve lesion in the acute phase of optic neuritis. It was associated with symptoms and signs of an optic neuropathy (impaired acuity and colour vision, an afferent pupillary defect and pain on eye movement) and with a reduction in amplitude and an increase in latency of the pattern VEP. The disappearance of Gd-DTPA leakage at follow-up was associated with a recovery of the amplitude of the VEP to a mean value about half that of the response from the asymptomatic eye, and with resolution of the clinical features. Secondly, the VEP amplitude and latency changes during the acute stage showed no correlation with the length of the lesion or the length of Gd-DTPA leakage, but at follow-up, the persistent reduction in amplitude did correlate inversely with lesion length on non-contrast MRI.

The duration of enhancement in these acute optic nerve lesions (usually less than 1 mth) is similar to that reported in new brain lesions in patients with clinically definite MS (Miller *et al.*, 1988*a*; Bastianello *et al.*, 1990; Kappos *et al.*, 1990; Harris *et al.*, 1991; Thompson *et al.*, 1991), and the results help to illuminate a long-standing problem in the pathophysiology of MS: the explanation of the time course of relapse and the mechanism of remission so characteristic of the early stages of the disease.

The particular advantages of studying optic neuritis in tackling pathophysiological questions have already been mentioned; the symptoms and signs are readily recognized and quantified and conduction can be easily monitored by VEPs. Caution must be exercised in using the known properties of demyelinated nerve fibres to interpret evoked potentials which depend on the integrity of both the conduction pathway and numerous

TABLE 2. AMPLITUDE IN MICROVOLTS AND LATENCY IN MILLISECONDS OF P100 COMPONENT IN PATTERN REVERSED VEP AT FIRST AND SECOND MRI

Patient			*First recording*				*Follow-up*			
			Amplitude		*Latency*		*Amplitude*		*Latency*	
No.	*Sex*	*ON*	*L eye*	*R eye*	*L eye*	*R eye*	*L eye*	*R eye*	*L eye*	*R eye*
1	F	L	8.1§	19.6	140§	100	4.6	19.5	130	104
2	M	B	2.2§	1.6§	123§	136§	9.7	10.0	117	118
3	F	R	10.2	2.7§	106	148§	10.3	4.6	105	115
4	M	B	Absent§	Absent§	–§	–§	No follow up			
5	F	L	3.2§	19.0	106§	118*	13.3	17.0	130	125*
6	F	L	8.3§	17.4	125§	104	No follow up VEP			
7	F	R	10.2	1.3§	101	110$^{+\S}$	11.5	5.2§	102	131§
8	F	L	Absent§	11.5	–§	104	9.2	7.8	138	113
9	F	L	2.9§	13.5	153§	106	7.0	14.8	126	106
10	M	L	1.6§	16.0	159§	109	3.3	14.2	145	110
11	F	R	11.8	9.6	118*	145§	15.4	11.5	119*	131

Abnormal responses underlined; * = abnormal response in asymptomatic eye; § = leaking optic nerve lesion at time of VEP; $^{+}$ = increased inter-ocular latency difference.

TABLE 3. MEAN AMPLITUDE (μV) AND LATENCY (ms) OF P100 COMPONENT OF THE PATTERN REVERSAL VEP IN 8 SYMPTOMATIC EYES OF 7 PATIENTS WHOSE OPTIC NERVE LESION DISPLAYED Gd-DTPA LEAKAGE AT THE FIRST RECORDING BUT NOT AT FOLLOW-UP

	Amplitude	*Latency*
First recording	4.2 ± 3.2	140.9 ± 17.0
Follow-up	7.8 ± 3.9	133.1 ± 11.3

Amplitude difference: $P = 0.02$; latency difference: $P = 0.1$, paired t test; cases included in this group: 1, 2, 3, 5, 9, 10 and 11; *Case 8* had an absent response at the first recording, and *Case 7* still displayed Gd-DTPA leakage at follow-up and therefore both were excluded from this group.

synapses from retina to visual cortex. Nevertheless, there is good evidence that a rapidly reversible decrease in amplitude is principally due to conduction block and that slowing of conduction in partially demyelinated nerve fibres contributes to delay in evoked potentials (McDonald and Sears, 1970; Halliday and McDonald, 1977; Persson and Sachs, 1981). Other consequences of demyelination probably also contribute to the latter. They include the development of very slow conduction in persistently demyelinated axons (Bostock and Sears, 1978; Bostock and McDonald, 1982) and delay in generation of the cortical response as a result of a reduced and dispersed input deriving from conduction block and unequal slowing in different fibres. Dispersion would also contribute to the reduction in amplitude.

It is well known that in the acute stage of optic neuritis there is both a decrease in amplitude and an increase in latency of the VEP and that in the recovery phase the amplitude recovers (though not completely) but the delay persists (Halliday *et al.*, 1973).

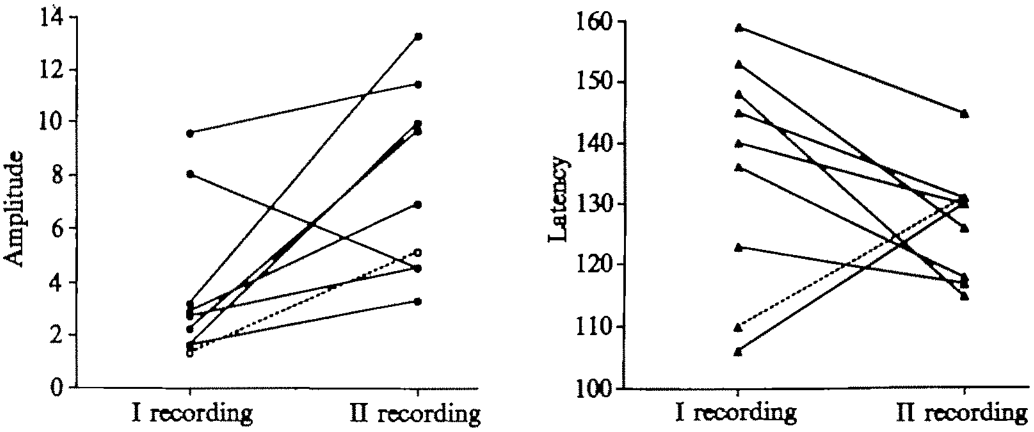

FIG. 4 Serial VEP P100 amplitude (μV) and latency (ms) changes in 9 symptomatic eyes (8 patients) ●—●, ▲—▲ = lesions leaking at first scan but not at follow-up, ○···○, △···△ = lesion leaking on both scans.

The use of Gd-DTPA as an MRI enhancing agent now allows us to interpret these findings more precisely in pathological terms. There is good evidence that recent MS lesions at post-mortem are characterized by inflammation and demyelination (Adams, 1989; Allen, 1991) and that Gd-DTPA leakage reflects the former (Guy *et al.*, 1990; Hawkins *et al.*, 1990; Katz *et al.*, 1990). It is the earliest detectable change in a new lesion and ceases after about a month (Miller *et al.*, 1988*a*; Bastianello *et al.*, 1990; Kappos *et al.*, 1990; Kermode *et al.*, 1990; Harris *et al.*, 1991; Thompson *et al.*, 1991).

Taking the evidence together we conclude, as others have, that demyelination is an early feature of the new lesion in optic neuritis and that it is still present after a month since the VEP is still delayed. Of particular interest is our finding that the recovery of amplitude (and vision) is associated with a cessation of leakage, i.e. resolution of inflammation. Our inability, using current techniques, to quantify the permeability of the blood-optic nerve barrier prevented us from detecting a graded relationship between amplitude and inflammation which would have established a causal connection between the two. Nevertheless, our results makes it likely that inflammation is the crucial factor in determining the reversible element of the conduction block.

How it does so is an open question. Several factors may contribute. Oedema is a prominent feature of acute MS lesions (Adams, 1989; Thompson *et al.*, 1991) and swelling of the optic nerve in optic neuritis is sometimes seen on CT or MRI (Mikol *et al.*, 1980; McCrary *et al.*, 1987; Miller *et al.*, 1988*b*; B. Youl and I. Moseley, unpublished observations). The anatomy of the nerve with its fibrous septa and its passage through the bony optic canal which it almost fills probably limits expansion and leads to the addition of a compressive element to the effects of demyelination in acute lesions. Pressure block which is rapidly reversible occurs in both peripheral and central nerve fibres (Lewis *et al.*, 1931; Merrington and Nathan, 1949; Kayan and Earl, 1975; Gutin *et al.*, 1980). More severe pressure can lead to demyelination or axonal loss (Ochoa *et al.*, 1972; Clifford-Jones *et al.*, 1985). In favour of such a mechanism sometimes operating in optic neuritis is the significant relationship between involvement of the

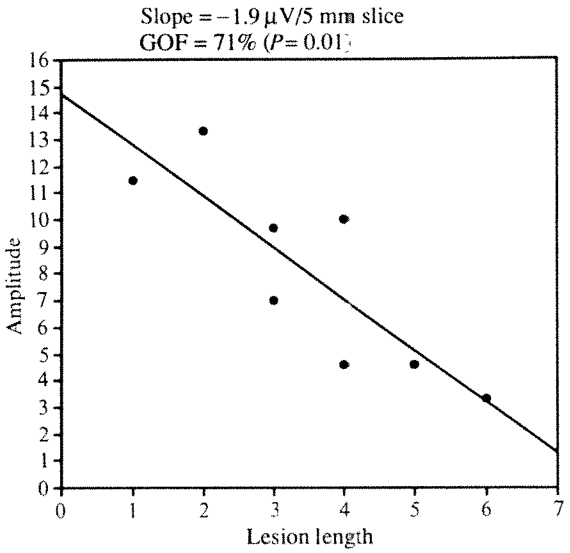

FIG. 5. Correlation of P100 amplitude (μV) with unenhanced lesion length (number of slices) on follow-up examination. GOF = goodness of fit.

optic nerve in the canal and delayed or incomplete recovery, implying irreversible axonal damage, perhaps on a vascular basis (Miller *et al.*, 1988*b*). It is also possible that cytokines released in inflammation interfere with conduction directly, or by inducing demyelination. Tumour necrosis factor produces a decline in membrane potential of muscle (Tracey *et al.*, 1986) and induces demyelination *in vitro* (Selmaj and Raine, 1988).

Turning to the origin of the clinical features of optic neuritis we have found a clear relationship between Gd-DTPA leakage, impairment of acuity and colour vision, an afferent pupillary defect and pain. The visual loss can be accounted for by the accompanying conduction block and its remission by recovery of conduction. The pain probably arises from the stimulation of nerve endings in the meningeal sheath and fibrous septa of the nerve (Hogan *et al.*, 1971) by pressure and pain mediators released during inflammation, as in peripheral nerve (Thomas, 1974; Asbury and Fields, 1984). The characteristic increase in pain on eye movement is probably due to the resulting increase in tension on the inflamed optic nerve at the extremes of gaze (Liu *et al.*, 1990).

The lack of correlation between length of lesion (with or without Gd-DTPA leakage) and latency of the VEP deserves comment. Though at first sight surprising it is less so when one considers the origin of the abnormal signal on MRI. In the acute lesion it is derived principally from vasogenic oedema due to impairment of the blood-brain barrier and in the chronic lesion from a combination of gliosis and a persistent increase in extracellular water (Barnes *et al.*, 1986, 1987, 1991; Miller *et al.*, 1988*a*). Demyelination *per se* is not visible on conventional proton MRI. Moreover, the present method of measurement is crude (maximum resolution 5 mm). Characteristically the acute MRI lesion in MS shrinks markedly (Willoughby *et al.*, 1989) after Gd-DTPA leakage ceases, leaving a smaller residual lesion which changes little unless reactivation of inflammation occurs (Thompson *et al.*, 1991). It is therefore of interest that we did find a significant inverse relationship between the length of the residual (non-leaking) lesion and amplitude. The longer a lesion the more internodes will be damaged and the greater the chance of conduction block (Rasminsky, 1973). Our previous observation that longer optic nerve lesions in optic neuritis are associated with a poorer visual outcome (Miller *et al.*, 1988*b*) is also consistent with this pathophysiological explanation.

In conclusion, we envisage the following sequence of events in the acute attack of optic neuritis. A focal area of inflammation develops around venules in the optic nerve and is accompanied by an increase in permeability of the blood-nerve barrier. The release of inflammatory mediators and the development of oedema leads to pain which is increased by changes in tension on the nerve during eye movement. Demyelination occurs at about the same time, though the precise order of events is unknown. Both inflammation and demyelination produce conduction block which results in impairment of vision. The inflammation resolves within a few weeks, with the relief of pain and (though not completely) the conduction block. As a result vision improves. The persistent defect in amplitude of the VEP is probably due to a combination of persisting demyelination and the abnormal conduction which accompanies it (block, slowing and dispersion). These conduction defects account for the visual defects (in fields, colour vision, contrast sensitivity and motion perception) which can be detected in many apparently recovered individuals. Latency ultimately returns to normal in only about 10% of adults (Halliday, 1982) but in more than 50% of childhood cases of optic neuritis (Kriss *et al.*, 1988). Remyelination (Prineas and Connell, 1979; Prineas *et al.*, 1987) has probably occurred in these cases. The time course of the clinical and MRI features of a typical episode of optic neuritis is similar to that of many relapses of MS due to lesions in other parts of the central nervous system and it seems likely that an important factor in remission from them too is the resolution of inflammation. Other factors which influence the later stages of recovery are reviewed elsewhere (Thompson and McDonald, 1991).

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REFERENCES

ADAMS CWM (1989) *A Colour Atlas of Multiple Sclerosis and other Myelin Disorders*. London: Wolfe Medical.

ALLEN IV (1991) Pathology of multiple sclerosis. In: *McAlpine's Multiple Sclerosis*. Second edition. Edited by W. B Matthews, A Compston, I. V. Allen and C. N. Martyn. Edinburgh: Churchill Livingstone, pp. 341–378.

ASBURY AK, FIELDS HL (1984) Pain due to peripheral nerve damage: an hypothesis. *Neurology, Cleveland*, **34**, 1587–1590.

BARNES D., MCDONALD WI, TOFTS PS, JOHNSON G, LANDON DN (1986) Magnetic resonance imaging of experimental cerebral oedema. *Journal of Neurology, Neurosurgery, and Psychiatry*, **49**, 1341–1347.

BARNES D, MCDONALD WI, JOHNSON G, TOFTS PS, LANDON DN (1987) Quantitative nuclear magnetic resonance imaging: characterisation of experimental cerebral oedema *Journal of Neurology, Neurosurgery, and Psychiatry*, **50**, 125–133.

Barnes D, Munro PMG, Youl BD, Prineas JW, McDonald WI (1991) The longstanding MS lesion: a quantitative MRI and electron microscopic study. *Brain*, **114**, 1271–1280.

Bastianello S, Pozzilli C, Bernardi S, Bozzao L, Fantozzi LM, Buttinelli C *et al.* (1990) Serial study of gadolinium-DTPA MRI enhancement in multiple sclerosis. *Neurology, Cleveland*, **40**, 591–595.

Bostock H, Sears TA (1978) The internodal axon membrane: electrical excitability and continuous conduction in segmental demyelination. *Journal of Physiology, London*, **280**, 273–301.

Bostock H, McDonald WI (1982) Recovery and function after demyelination. In: *Neuronal-Glial Cell Interrelationships*. Edited by T. A. Sears. Berlin: Springer-Verlag, pp. 287–301.

Clifford-Jones RE, McDonald WI, Landon DN (1985) Chronic optic nerve compression: an experimental study. *Brain*, **108**, 241–262.

Compston DAS, Batchelor JR, Earl CJ, McDonald WI (1978) Factors influencing the risk of multiple sclerosis developing in patients with optic neuritis. *Brain*, **101**, 495–511.

Grossman RI, Gonzalez-Scarano F, Atlas SW, Galetta S, Silberberg DH (1986) Multiple sclerosis: gadolinium enhancement in MR imaging. *Radiology*, **161**, 721–725.

Gutin PH, Klemme WM, Lagger RL, MacKay AR, Pitts LH, Hosobuchi Y (1980) Management of the unresectable cystic craniopharyngioma by aspiration through an Ommaya reservoir drainage system. *Journal of Neurosurgery*, **52**, 36–40.

Guy J, Fitzsimmons J, Ellis EA, Mancuso A (1990) Gadolinium-DTPA-enhanced magnetic resonance imaging in experimental optic neuritis. *Ophthalmology*, **97**, 601–607.

Halliday AM (1982) *Evoked Potentials in Clinical Testing*. Edinburgh: Churchill Livingstone.

Halliday AM, McDonald WI, Mushin J (1973) Delayed pattern-evoked responses in optic neuritis in relation to visual acuity. *Transactions of the Ophthalmological Society of the United Kingdom*, **93**, 315–324.

Halliday AM, McDonald WI (1977) Pathophysiology of demyelinating disease. *British Medical Bulletin*, **33**, 21–27.

Harris JO, Frank JA, Patronas N, McFarlin DE, McFarland HF (1991) Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: implications for clinical trials and natural history. *Annals of Neurology*, **29**, 548–555.

Hawkins CP, Munro PMG, MacKenzie F, Kesselring J, Tofts PS, du Boulay EPGH *et al.* (1990) Duration and selectivity of blood-brain barrier breakdown in chronic relapsing experimental allergic encephalomyelitis studied by gadolinium-DTPA and protein markers. *Brain*, **113**, 365–378.

Hogan MJ, Alvarado JA, Weddell JE (1971) *Histology of the Human Eye: An Atlas and Textbook*. Philadelphia and London: W. B. Saunders.

Kappos L, Gold R, Hofmann E, Keil W, Clauß W (1990) Multiple sclerosis: diagnostic criteria and the role of contrast-enhanced MRI. In: *Contrast Media in MRI*. Edited by E. M. Bydder, R. Felix, E. Bücheler, B. P. Drayer, H. P. Niendorf, M. Takahashi *et al.* Berlin: Medicome Europe, pp. 127–135.

Katz D, Taubenberger J, Raine C, McFarlin D, McFarland H (1990) Gadolinium-enhancing lesions on magnetic resonance imaging: neuropathological findings. *Annals of Neurology*, **28**, 243.

Kayan A, Earl CJ (1975) Compressive lesions of the optic nerves and chiasm: pattern of recovery of vision following surgical treatment. *Brain*, **98**, 13–28.

Kermode AG, Thompson AJ, Tofts P, MacManus DG, Kendall BE, Kingsley DPE *et al.* (1990) Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis: pathogenetic and clinical implications. *Brain*, **113**, 1477–1489.

Kriss A, Francis DA, Cuendet F, Halliday AM, Taylor DSI, Wilson J *et al.* (1988) Recovery after optic neuritis in childhood. *Journal of Neurology, Neurosurgery, and Psychiatry*, **51**, 1253–1258.

Lassman H (1983) *Comparative Neuropathology of Chronic Experimental Allergic Encephalomyelitis and Multiple Sclerosis*. Berlin: Springer Verlag.

Lewis T, Pickering GW, Rothschild P (1931) Centripetal paralysis arising out of arrested bloodflow to limb, including notes on form of tingling. *Heart*, **16**, 1–32.

Liu CSC, Youl BD, Moore SM, Moseley IF (1990) MRI enables demonstration of position of optic nerves on extremes of eye movement. *Ninth Annual Meeting of the Society for Magnetic Resonance in Medicine, Book of Abstracts*, **II**, 631.

LUKES SA, CROOKS LE, AMINOFF MJ, KAUFMAN L, PANITCH HS, MILLS C *et al.* (1983) Nuclear magnetic resonance imaging in multiple sclerosis. *Annals of Neurology*, **13**, 592–601.

MCCRARY JA, DEMER JL, FRIEDMAN DI, MAWAD MM (1987) Computed tomography and magnetic resonance imaging in the diagnosis of inflammatory disease of the optic nerve. *Survey of Ophthalmology*, **31**, 352–355.

MCDONALD WI, SEARS TA (1970) The effects of experimental demyelination on conduction in the central nervous system. *Brain*, **93**, 583–598.

MERRINGTON WR, NATHAN PW (1949) A study of post-ischaemic paraesthesiae *Journal of Neurology, Neurosurgery, and Psychiatry*, **12**, 1–18.

MIKOL F, BOUCHAREINE A, AUBIN ML, VIGNAUD J (1980) La tomodensitométrie dans la sclérose en plaques. *Revue Neurologique*, **136**, 481–490.

MILLER DH, RUDGE P, JOHNSON G, KENDALL BE, MACMANUS DG, MOSELEY IF *et al.* (1988*a*) Serial gadolinium enhanced magentic resonance imaging in multiple sclerosis. *Brain*, **111**, 927–939.

MILLER DH, NEWTON MR, VAN DER POEL JC, DU BOULAY EPGH, HALLIDAY AM, KENDALL BE *et al.* (1988*b*) Magnetic resonance imaging of the optic nerve in optic neuritis. *Neurology, Cleveland*, **38**, 175–179.

NOSEWORTHY JH, GILBERT JJ, VANDERVOORT MK, KARLIK SJ (1988) Postnatal NMR changes in guinea pig central nervous system: potential relevance to experimental allergic encephalomyelitis. *Magnetic Resonance in Medicine*, **6**, 199–211.

OCHOA J, FOWLER TJ, GILLIATT RW (1972) Anatomical changes in peripheral nerves compressed by a pneumatic tourniquet. *Journal of Anatomy*, **113**, 433–455.

ORMEROD IEC, MILLER DH, MCDONALD WI, DU BOULAY EPGH, RUDGE P, KENDALL BE *et al.* (1987) The role of NMR imaging in the assessment of multiple sclerosis and isolated neurological lesions: a quantitative study. *Brain*, **110**, 1579–1616.

PATY DW, OGER JJF, KASTRUKOFF LF, HASHIMOTO SA, HOOGE JP, EISEN AA *et al.* (1988) MRI in the diagnosis of MS: a prospective study with comparison of clinical evaluation, evoked potentials, oligoclonal banding, and CT. *Neurology, Cleveland*, **38**, 180–185.

PERSSON HE, SACHS C (1981) Visual evoked potentials elicited by pattern reversal during provoked visual impairment in multiple sclerosis. *Brain*, **104**, 369–382.

PRINEAS JW, CONNELL F (1979) Remyelination in multiple sclerosis. *Annals of Neurology*, **5**, 22–31.

PRINEAS JW, KWON EE, SHARER LR, CHO E-S (1987) Massive early remyelination in acute multiple sclerosis. *Neurology, Cleveland*, **37**, Supplement 1, 109.

RASMINSKY M (1973) The effects of temperature on conduction in demyelinated single nerve fibers. *Archives of Neurology, Chicago*, **28**, 287–292.

RUNGE VM, PRICE AC, KIRSHNER HS, ALLEN JH, PARTAIN CL, JAMES AE (1984) Magnetic resonance imaging of multiple sclerosis: a study of pulse-technique efficacy. *AJR: American Journal of Roentgenology*, **143**, 1015–1026.

SELMAJ KW, RAINE CS (1988) Tumor necrosis factor mediates myelin and oligodendrocyte damage in vitro. *Annals of Neurology*, **23**, 339–346.

STEWART WA, HALL LD, BERRY K, PATY DW (1984) Correlation between NMR scan and brain slice data in multiple sclerosis. *Lancet*, **ii**, 412.

THOMAS PK (1974) The anatomical substratum of pain: evidence derived from morphometric studies on peripheral nerve. *Canadian Journal of Neurological Sciences*, **1**, 92–97.

THOMPSON AJ, KERMODE AG, MACMANUS DG, KENDALL BE, KINGSLEY DPE, MOSELEY IF *et al.* (1990) Patterns of disease activity in multiple sclerosis; clinical and magnetic resonance imaging study. *British Medical Journal*, **300**, 631–634.

THOMPSON AJ, KERMODE AG, WICKS D, MACMANUS DG, KENDALL BE, KINGSLEY DPE *et al.* (1991) Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Annals of Neurology*, **29**, 53–62.

THOMPSON AJ, MCDONALD WI (1991) Multiple sclerosis and its pathophysiology. In: *Diseases of the Nervous System.* Edited by A. K. Asbury, G. McKhann and W. I. McDonald. Philadelphia: W. B. Saunders. In press.

TRACEY KJ, LOWRY SF, BEUTLER B, CERAMI A, ALBERT JD, SHIRES GT (1986) Cachectin/tumor necrosis factor mediates changes of skeletal muscle plasma membrane potential. *Journal of Experimental Medicine*, **164**, 1368–1373.

WILLOUGHBY EW, GROCHOWSKI E, LI DKB, OGER J, KASTRUKOFF LF, PATY DW (1989) Serial magnetic resonance scanning in multiple sclerosis: a second prospective study in relapsing patients. *Annals of Neurology,* **25,** 43–49.

YOUL BD, MILLER DH, MACMANUS DG, MOORE SG, BARNES D, KERMODE A *et al.* (1991) Optic nerves show gadolinium enhancement in early optic neuritis. *Neuroradiology,* **33,** Supplement, 129–130.

YOUNG IR, HALL AS, PALLIS CA, LEGG NJ, BYDDER GM, STEINER RE (1981) Nuclear magnetic resonance imaging of the brain in multiple sclerosis. *Lancet,* **ii,** 1063–1066.

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Brain (1991), **114**, 2451–2463

ORIGIN OF THE SECONDARY INCREASE IN FIRING PROBABILITY OF HUMAN MOTOR NEURONS FOLLOWING TRANSCRANIAL MAGNETIC STIMULATION

STUDIES IN HEALTHY SUBJECTS, TYPE I HEREDITARY MOTOR AND SENSORY NEUROPATHY AND MULTIPLE SCLEROSIS

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SUMMARY

In tonically active human motor neurons serving upper limb muscles there is a late rise in firing probability following transcranial magnetic stimulation termed the secondary peak (SP). The aim was to study the mechanism of SP and the pathway that mediates it. For this purpose, the response to transcranial magnetic stimulation of 62 repetitively firing low threshold single motor units from upper limb muscles was studied with peri-stimulus time histograms in 8 healthy subjects and in 13 patients with either Type I hereditary motor and sensory neuropathy (HMSN) or multiple sclerosis (MS). Separate peri-stimulus time histograms, constructed for trials in which the motor unit fired in the primary peak (PP) and those in which it fired in SP, showed that SP was not caused by a resumption of firing after the preceding PP. In the first dorsal interosseous muscle, the observed increase in the interval between PP and SP in patients with either HMSN or MS, when compared with healthy subjects, suggested that the pathway mediating SP had both peripheral and central components. Evidence for a peripheral component was substantiated by the observed slope of the line relating the latency of SP in different upper limb muscles to peripheral conduction distance, which was more than 3 times greater than that for PP, and by comparisons in the same motor unit made between the latency of responses to finger taps and to transcranial magnetic stimulation. Evidence for the origin of SP was consistent with a long loop reflex, or with collateral activation of γ motor neurons and subsequent motor neuron firing from muscle afferent inputs. SP discharges were found to occur earlier than expected on the basis of the spontaneous motor unit firing rate, suggesting that SP was caused by the rising phase of an excitatory post-synaptic potential, rather than by the decay of an inhibitory post-synaptic potential.

INTRODUCTION

The discharge of tonically active single human motor units can be modulated by transcranial magnetic stimulation (Hess and Mills, 1986; Mills, 1988; Day *et al.*, 1989; Boniface *et al.*, 1991). The probability of a motor unit firing in the epoch of time surrounding a stimulus can be estimated using a peri-stimulus time histogram. In upper limb motor units from healthy subjects, two periods of raised firing probability occur

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after the stimulus; these have been termed the primary and secondary peaks (Boniface *et al.*, 1991).

The primary peak (PP) has an onset latency ranging from 13 ms in deltoid to 31 ms in the first dorsal interosseous muscle and has a short duration of 4.6 ± 1.7 ms (mean ± SD). These features combined with the finding that PP is multi-modal have lead to the suggestion that PP represents the arrival at the motor neuron of monosynaptic excitation transmitted by multiple descending volleys in fast conducting corticospinal fibres.

The secondary peak (SP) has different characteristics to PP: its onset latency in first dorsal interosseous muscle varies between motor units from 56–90 ms and it is more dispersed, having a mean duration of 20.9 ± 12.0 ms. SP is seen in other upper limb muscles including deltoid, biceps, brachioradialis and flexor carpi ulnaris (Mills *et al.*, 1991). The origin of this SP is unknown. In principle, a period of raised firing probability can be produced by either an excitatory post-synaptic potential at the motor neuron, or it can follow an inhibitory post-synaptic potential (Fetz and Gustafsson, 1983). SP could be mediated over a slow or multi-synaptic corticospinal pathway or it could be a manifestation of reflex afferent input to the motor neuron.

In this paper, the possible mechanisms and pathways for SP have been explored by examining patients with demyelinating peripheral neuropathy in whom the peripheral component of response latency is prolonged, and patients with multiple sclerosis (MS) in whom the central component is prolonged. Evidence suggests that SP is caused by the rising phase of a late excitatory post-synaptic potential and that the pathway mediating SP has both peripheral and central components. It is postulated that 2 candidates for such a pathway would be from the corticospinal tract via gamma motor neurons and peripheral afferents to the motor neuron, or a long loop reflex.

METHODS

The response to transcranial magnetic stimulation of a total of 62 low threshold repetitively firing single first dorsal interosseous muscle motor units of the right hand was studied with peri-stimulus time histograms in 8 healthy subjects (age 28–42 yrs) (20 motor units), 4 patients with Type I hereditary motor and sensory neuropathy (HMSN) (19–43 yrs) (6 motor units) and 9 patients with MS (35–58 yrs) (21 motor units). Fifteen motor units from other arm muscles of the right upper limb (deltoid, biceps, brachioradialis, flexor carp ulnaris, extensor digitorum communis) were also sampled in healthy subjects. MS patients were categorized according to Poser *et al.* (1983). All subjects were right handed. Informed consent was obtained and experiments were performed with the approval of the local ethics committee.

Transcranial magnetic stimulation was performed with the inducing current flowing in an anticlockwise direction in a circular coil (Novametrix 200, mean diameter 9 cm) positioned tangentially at the vertex. The characteristics of the magnetic stimulator, the method used for recording unitary responses to transcranial magnetic stimulation, the data analysis and the criteria used for defining peaks in the peri-stimulus time histogram are described in detail elsewhere (Hess *et al.*, 1987*a*; Boniface *et al.*, 1991). Stimuli were delivered at random with respect to the ongoing spike train (random stimulation experiments) at a maximum rate of 1 *per* 3 s, in up to 500 trials. At the start of each experiment, a short series of trials was undertaken to select a stimulus intensity high enough to cause the motor unit to discharge at the primary peak latency, but not so high as to produce many compound motor unit discharges. The stimulus intensities used ranged from 35–53% of the maximal output of the stimulator for healthy subjects, 45–50% for HMSN patients and 50–73% for MS patients. Epochs of 500 ms were recorded, with a post-stimulus period of 250 ms for healthy subjects and MS patients, and 400 ms for HMSN patients. For 1 motor unit, magnetic stimuli were delivered at a fixed interval of 10 ms after a preceding voluntary discharge (spike-triggered experiment). This motor unit and 1 other were also studied while mechanical taps were applied to the index finger (*see below*). All subjects were given auditory and visual feedback of the motor unit discharge and were asked to keep the firing frequency as steady as possible without recruiting additional motor units, but neither the force of contraction nor the precise firing rate were controlled.

In 4 motor units from 3 healthy subjects, peri-stimulus time histograms were obtained on line while mechanical taps were applied to the first interphalangeal joint of the index finger. The taps consisted of a rectangular pulse of duration 1–2 ms which produced an adduction movement of the index finger (600–1000 trials). For 2 of these motor units (motor unit 1—random stimulation experiment and motor unit 2—spike-triggered experiment) peri-stimulus time histograms were also constructed following transcranial magnetic stimulation. The distance from the spine of the seventh cervical vertebra to the electrode site in first dorsal interosseous muscle for motor units 1 and 2 was 76 cm (2 subjects). The same distance measured for the 3 subject groups was 73–86 cm for healthy controls, 73–82 cm for HMSN patients and 73–79 cm for MS patients.

Central motor conduction time was estimated in HMSN patients by determining the latency of at least 4 surface-recorded responses from first dorsal interosseous muscle and subtracting: (F wave latency + M wave latency – 1)/2 (Hess *et al.*, 1987*b*).

RESULTS

All of the HMSN patients had characteristic clinical features. None had physical signs referrable to the central nervous system. Motor conduction velocity in the forearm segment of the ulnar nerve was reduced to 13–21 ms^{-1}. Central motor conduction time in the HMSN patients ranged from 7.5–8.15 ms (normal upper limit 8.3 ms). All 9 MS patients had upper motor neuron signs and first dorsal interosseous muscle was clinically weak in all but 1 patient who had ataxia of the upper limbs. In 2 MS patients there were sensory deficits affecting the right hand.

In first dorsal interosseous muscle motor units exhibiting both SP and PP, the pre-stimulus firing rate ranged from 4.8–11.0/s (mean 8.4) for motor units from healthy subjects, 4.1–12.8/s (mean 7.6) for HMSN patients and 5.6–10.8/s (mean 7.7) for MS patients. Sixteen motor units from healthy subjects were tested for serial correlation between consecutive interspike intervals in the pre-stimulus period, which was not found to be significant except in 1 motor unit.

For each motor unit, the series of trials could be sorted into those containing a discharge with PP (primary peak trials) and those without (non-primary peak trials). Alternatively, trials could be sorted into those containing a discharge within SP (secondary peak trials) and those without (non-secondary peak trials). Furthermore, because it was usually the case that if the motor unit fired in PP, it did not do so in SP and vice versa, trials could be sorted into 3 groups: primary peak trials, secondary peak trials and non-primary peak–non-secondary peak trials (Fig. 1). In all subjects, peri-stimulus time histograms constructed for primary peak trials and for secondary peak trials showed that SP was not caused by a resumption of firing after PP. Only in 3 motor units was SP marginally overlapped by the peak caused by the resumption of firing after PP. These motor units were not included in the analysis of SP.

Healthy subjects

PP was present in all the motor units studied. SP was present in 55% of first dorsal interosseous muscle motor units (Fig. 2A) and 60% of motor units from other arm muscles, according to a rigorous definition for SP (Boniface *et al.*, 1991). For those first dorsal interosseous muscle motor units, where both PP and SP were present, PP had a peak latency of 24–32 ms. SP had a peak latency of 63–98 ms and a duration

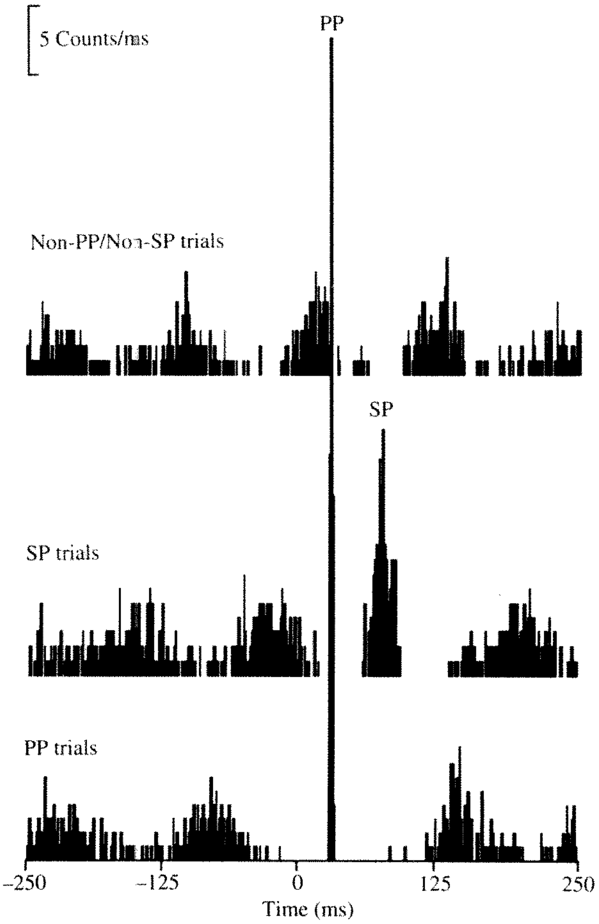

FIG. 1. Results from 1 motor unit (500 trials) sorted into 3 peri-stimulus time histograms showing the primary peak trials (*lower*), the secondary peak trials (*middle*) and the remaining non-primary peak–non-secondary peak trials (*upper*). The peri-stimulus time histograms are vertically aligned and constructed on the same scale to allow direct comparison of the latency and size of peaks. Consequently, PP extends from the abscissa for PP trials to the top of the figure, passing through the other 2 peri-stimulus time histograms. The peak caused by the resumption of firing after PP is seen to occur later than SP. Bin width = 1 ms, stimuli are at time = 0.

of 5–39 ms. The intermodal primary peak–secondary peak interval ranged from 39–71 ms, with a mean of 54 ms (Fig. 3).

Peripheral mechanical stimulation and transcranial magnetic stimulation in the same motor unit. Following finger taps (rectangular pulse, muscle stretch) peaks were evident in the peri-stimulus time histogram at peak latencies of 41 ms, 35 ms, 46 ms and 44 ms, with durations of 8 ms, 5 ms, 6 ms and 6 ms for motor units 1, 2, 3 and 4, respectively. A second peak was also evident in the peri-stimulus time histogram of motor unit 1 (peak latency 74 ms) and in motor unit 2 (peak latency 61 ms) (Fig. 4). No second peak was evident in the peri-stimulus time histograms from the remaining 2 motor units (motor units 3 and 4). Following transcranial magnetic stimulation in motor units 1 and 2, PP had a peak latency of 29 ms and 28 ms, and SP had a peak latency of 91 ms and 71 ms for motor units 1 and 2, respectively. The corresponding primary peak–secondary peak intervals were therefore 62 ms and 43 ms.

Latency of secondary peak and primary peak discharges in relation to peripheral conduction distance. The peak latency of PP and SP were both positively correlated with the distance from the spine of the C7 vertebra to the electrode site in the muscle

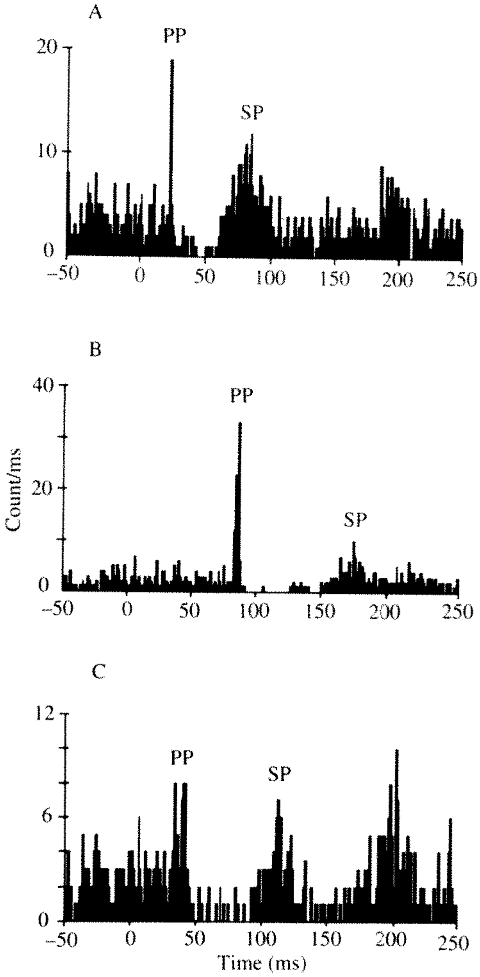

FIG. 2. Peri-stimulus time histograms from a healthy subject (A), a patient with hereditary motor and sensory neuropathy (HMSN) (B) and a patient with MS (C) (363, 96 and 77 trials). The peak latencies of SP are 84 ms, 169 ms and 110 ms, respectively. The latency of PP in B and the latency of SP in B and C is delayed when contrasted with A, and the interval between PP and SP in B and C is also increased. Peaks at 200 ms in A and C were probably caused by synchronization of discharges following SP. Bin width = 1 ms, stimuli are at time = 0.

($P < 0.001$, $P < 0.005$, respectively, Spearman ϱ) (Fig. 5). The slope relating the peak latency of SP to distance (0.57 ms/cm) was found to be significantly greater than that relating the peak latency of PP to distance (0.17 ms/cm) ($P < 0.01$).

The effect of magnetic stimuli on interspike interval when contrasted with simulated control stimuli. The relationship between stimulus-spike interval (discharge latency) and spike-stimulus interval (interval between the stimulus and the preceding voluntary discharge) was plotted for simulated stimuli introduced during the pre-stimulus period. This produced a distribution with an equal number of points about a line representing the median pre-stimulus interspike interval (Fig. 6C). The equivalent graph for magnetic stimuli showed 2 clusters corresponding to SP and PP (Fig. 6B). In contrast to Fig. 6C, there was an unequal distribution in the number of points about the same line for the median pre-stimulus interspike interval. Within the cluster corresponding to SP, there was an increase in the number of points to the left of the median line and a decrease in the number of points to the right.

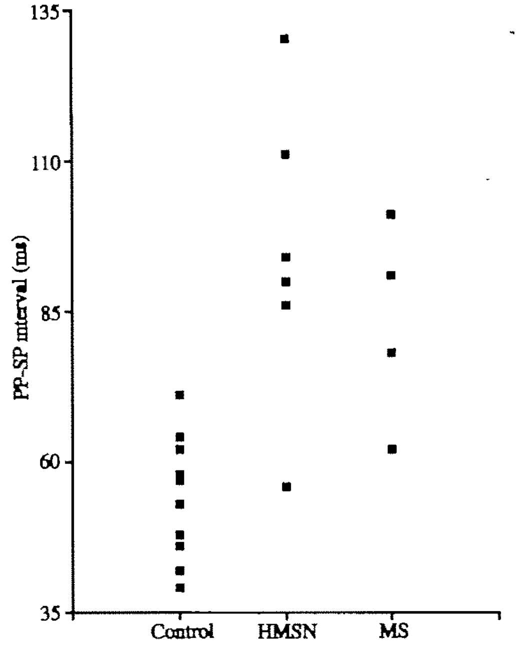

FIG. 3 Intermodal interval between PP and SP shown for healthy subjects, patients with hereditary motor and sensory neuropathy (HMSN) and patients with MS. In all but 2 motor units, the primary peak—secondary peak interval in both patient groups was greater than the maximum primary peak—secondary peak interval observed in healthy controls.

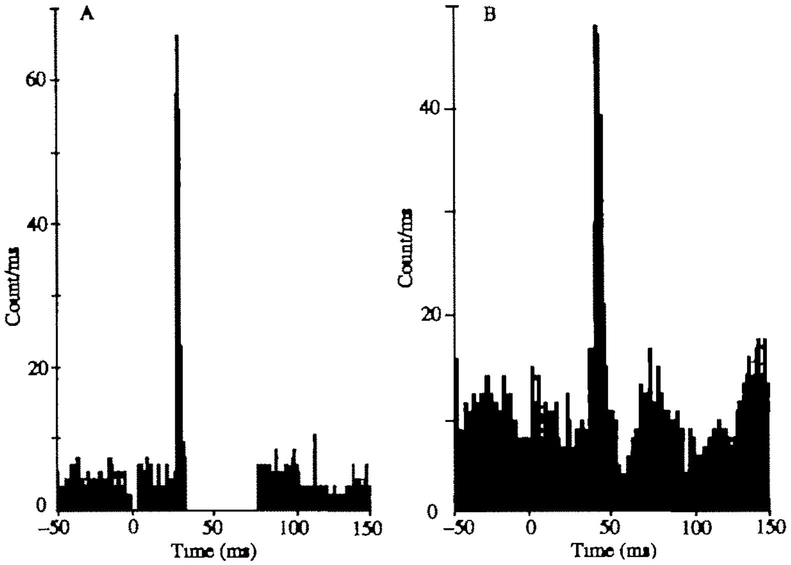

FIG 4. Two peri-stimulus time histograms from the same motor unit. A, the peri-stimulus time histogram following transcranial magnetic stimulation shows PP and SP (162 trials). The modal latencies of PP and SP were 29 ms and 91 ms, respectively B, mechanical taps to the index finger also produced 2 increases in firing probability (1000 trials). The model latency of the first peak was 41 ms and that of the second peak was 74 ms. Bin width = 1 ms, stimuli are at time = 0. In A, the small gap near time zero in the peri-stimulus time histogram was caused by stimulus artefact.

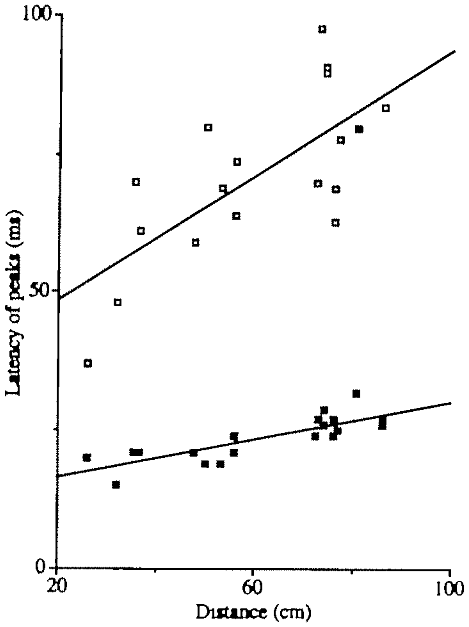

FIG. 5 The peak latencies of both PP (closed squares) and SP (open squares) are significantly correlated with the distance from the spine of the C7 vertebra to the electrode site ($P < 0.001$, $P < 0.005$, respectively, Spearman ϱ). The slope relating SP to distance (0.57 ms/cm) is significantly greater than that relating PP to distance (0.17 ms/cm) ($P < 0.001$).

HMSN and MS patients

In HMSN patients, PP and SP were present in all the motor units studied (Figs 2B, 7). PP had a peak latency of 56–83 ms and SP had a peak latency of 132–197 ms, with a duration of 14–44 ms. The primary peak–secondary peak interval ranged from 59–130 ms, with a mean of 95 ms (Fig. 3).

In MS patients, PP was present in all the motor units studied and SP was present in 19% of the motor units (Fig. 2C). For those motor units where both PP and SP were present, PP had a peak latency of 21–38 ms and SP had a peak latency of 92–129 ms, with a duration of 20–48 ms. The primary peak–secondary peak interval ranged from 62–101 ms, with a mean of 82 ms (Fig. 3).

DISCUSSION

Two fundamental questions will be addressed concerning the secondary rise in motor unit firing probability in response to magnetic stimuli: over which pathways is it mediated and by what mechanism is it produced?

The possible pathways mediating SP are illustrated in Fig. 8: A shows a corticospinal pathway, different from that which transmits the primary excitatory response, which involves more slowly conducting fibres and/or more synapses. In Fig. 8B,C a reflex from the periphery is shown, deriving from motor units other than the one recorded and transmitted over a segmental (Fig. 8B) or supra-segmental (Marsden *et al.*, 1976) route (Fig. 8C). In Fig. 8D activation of γ or possibly β motor neurons by the descending volley (Grigg and Preston, 1971; Rothwell *et al.*, 1990) produces subsequent motor neuron firing from muscle afferent inputs. We cannot assume, however, that a single

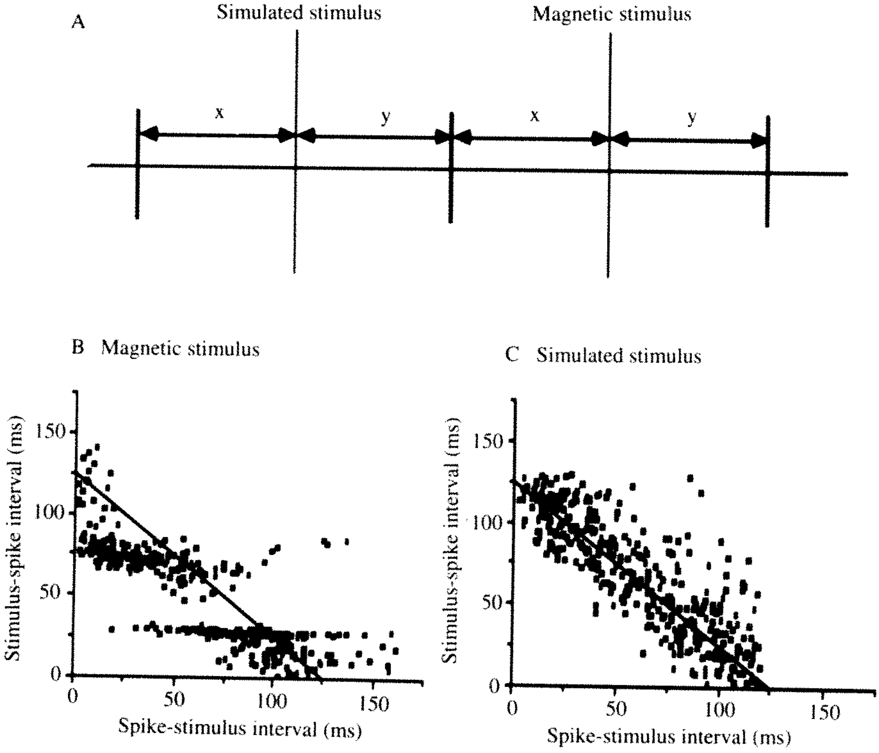

FIG. 6. The effect of magnetic stimuli on the duration of interspike intervals when compared with simulated control stimuli suggests that secondary peak and primary peak discharges occur earlier than expected. A, diagram of a train of 3 spikes with magnetic and simulated stimuli, x represents the spike-stimulus interval, y the stimulus-spike interval. In B and C the stimulus-spike interval (y) is plotted against the spike-stimulus interval (x) for data from a random stimulation experiment (n = 414 trials). In B, magnetic stimuli have caused a clustering of points corresponding to PP and SP at stimulus-spike intervals in the region of 25 ms and 75 ms, respectively. As a control, C shows a similar graph plotted from the same experiment in which simulated stimuli were introduced during the period before the magnetic stimulus. The points occur in equal number about the oblique line which represents the median pre-stimulus interspike interval (124 ms). The same line is also shown in B. In B, points to the left of the oblique line are therefore derived from interspike intervals that were shorter than the median pre-stimulus interspike interval. These are increased in number in the clusters that correspond to PP and SP, when contrasted with C.

mechanism is involved; it is conceivable that the motor neuron is caused to fire in SP by the relatively synchronous generation of post-synaptic potentials from both central and peripheral sources. The possibility that SP merely represents the resumption of firing of motor units that have discharged at the primary peak latency has been excluded by consideration of sorted peri-stimulus time histograms (Fig. 1).

We have shown that the peak latencies of both PP and SP are positively correlated with distance from the spinal cord (Fig. 5). The fact that the slope of this relationship for SP is 3 times steeper than that for PP suggests that the secondary peak latency has a peripheral nerve conduction component. Otherwise we would have to postulate that the possible central pathway to proximal muscles was considerably faster or had fewer synapses than that to distal muscles; this seems unlikely. The latency difference between

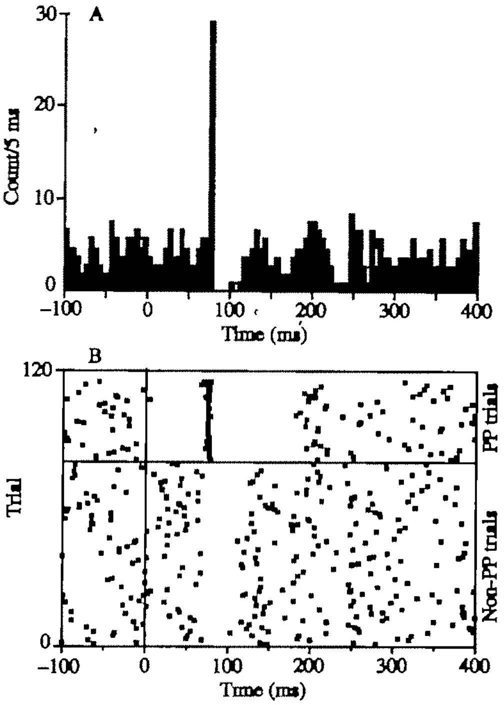

FIG. 7. Results from a patient with hereditary motor and sensory neuropathy (HMSN) (119 trials). A, the modal latencies of PP and SP were 76 ms and 132 ms, respectively. These latencies are both prolonged when contrasted with healthy subjects. The primary peak–secondary peak interval of 59 ms is, however, within the normal range (*see* Discussion). Bin width = 1 ms, stimuli are at time = 0. B, raster plot of the same data, sorted for primary peak trials (*upper panel*) and non-primary peak trials (*lower panel*) The resumption of firing after PP contributes to the late peak in the peri-stimulus time histogram in the region of 200 ms, but not to SP. Each point represents 1 discharge.

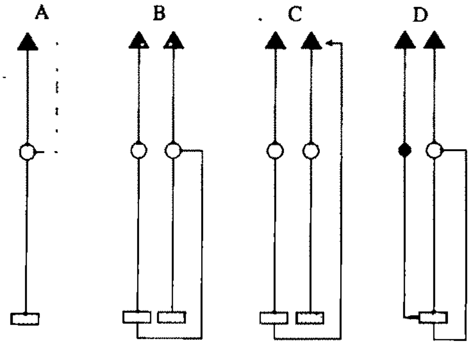

FIG. 8. Diagram illustrating the possible pathways that mediate SP: (A) corticospinal pathway, different from that which transmits the primary excitatory response, involving more slowly conducting fibres and/or more synapses (dotted line); (B) reflex from the periphery deriving from motor units other than the one recorded and transmitted over a segmental route; (C) reflex as in (B) but transmitted over a suprasegmental route; (D) activation of γ motor neurons by the descending volley and subsequent motor neuron firing from muscle afferent inputs. Triangle = corticospinal cell; open circle = cell body of alpha motor neuron; open block = index motor unit; closed block = another motor unit in the same muscle; closed circle = gamma motor neuron.

SP and PP observed in healthy subjects is consistent with possibilities A, B and C (Fig. 8) if we assume γ axon conduction velocity to be about half that of the alpha axons and 1a afferent conduction velocity to be about the same as motor axon velocity.

In patients with HMSN, the peripheral nerve conduction velocity in myelinated fibres was considerably reduced but central motor conduction time was within the range of normal. Thus, if SP is mediated over a peripheral nerve pathway, its latency should be delayed in HMSN. Conversely, if it is mediated by a purely central pathway, we anticipate SP at the normal interval after PP. We find, with one exception (*see below*), that SP is considerably delayed after PP, implicating a peripheral component in the pathway. Again the latency of SP is consistent with possibilities B, C, and D (Fig. 8) if we assume proportionally reduced velocity in γ and Ia axons.

It is of interest that all motor units from patients with HMSN exhibited SP. This is likely to be due to the fact that SP is delayed beyond the period of zero firing probability that follows PP (*see also* Fig. 9).

In one motor unit from a patient with HMSN, the primary peak was at 76 ms (of which 70 ms would be due to peripheral delay) and a secondary peak was evident after an interval of only 59 ms (Fig. 7). Even if we assume that afferent axons have *normal* conduction velocity, there is insufficient time for these discharges to have been mediated by a reflex mechanism. In fact, the fastest motor axons in this patient conducted at only 13 ms^{-1}. This leads us to the conclusion that this particular peak must have been mediated over a second central pathway (Fig. 8A).

Further evidence that the pathway mediating SP has a central component comes from a consideration of motor unit responses in patients with MS. Here the peripheral nerve conduction velocity was normal but central pathways may have been demyelinated. If SP were mediated purely over a peripheral pathway, we would anticipate the primary peak–secondary peak intervals to be within the normal range. In 3 of 4 motor units, the primary peak–secondary peak intervals were longer than those encountered in healthy controls, and in 1 of these 3 motor units the primary peak latency was also greater than in the healthy controls. These findings would be consistent with Fig. 8C. The latency for the afferent pathway when estimated for some motor units from healthy subjects, however, would be shorter than expected (Gandevia and Burke, 1988). It is also unlikely that a spinal reflex pathway would cause the motor neuron to fire in SP only at a time when the afferent input was facilitated by a late descending input (i.e. a combination of Fig. 8A and B). In this case, the central pathway in HMSN patients would have to be pathologically slowed to an appropriate degree to allow the synchronized excitation of the motor neuron. An alternative possibility is Fig. 8D in which the central pathway to the γ motor neurons in healthy subjects conducted at a slower rate than the direct pathway to the index motor neuron, and was consequently disproportionately affected by demyelination in patients with MS.

We are thus led to the conclusion that the pathways mediating SP have both central and peripheral components. If SP is comparable with the rise in firing probability that occurred in first dorsal interosseous muscle motor units in response to mechanical pulses applied to the index finger (or to the belly of the muscle) in this and other studies (Stephens *et al.*, 1976; Buller *et al.*, 1980) then the primary peak–secondary peak interval would correspond to the conduction time from muscle to spinal cord to muscle. This is consistent with the gradient of the line relating secondary peak latency to distance from the cord, which is more than 3 times that relating primary peak latency to distance (Fig. 5). Furthermore, in the 2 motor units that were investigated with both transcranial magnetic stimulation and finger taps, the primary peak–secondary peak intervals (43 ms and 62 ms) were 8–21 ms longer than the modal latency of the first peak that occurred in response to finger taps in the same motor units (35 ms and 41 ms) and 17–29 ms longer than the interval between the first and second peaks (33 ms and 26 ms) that occurred in response to finger taps. If the primary peak–secondary peak intervals had been shorter than the data obtained from mechanical stimuli in the same motor unit, this would not have supported the proposed peripheral component in the pathway for

SP. Future studies may enable SP to be attributed to either excitation of 1a afferents from the agonist muscle by γ motor neuron discharge; excitation of 1b afferents from a contraction of the antagonist; or defacilitation of 1 b afferents from the agonist.

A rise in firing probability, such as SP, may be due to the rising phase of an excitatory post-synaptic potential (Knox and Poppele, 1977) or to the decay of an inhibitory post-synaptic potential (Fetz and Gustafsson, 1983) or a combination of both. Excitatory post-synaptic potentials and inhibitory post-synaptic potentials are both detected in spinal motor neurons of the monkey following surface and intracortical electrical stimulation of the motor cortex (Phillips and Porter, 1977). In principle, inferences regarding the polarity of the post-synaptic potential underlying SP could be drawn from a statistical comparison of serial interspike intervals (Tuckwell, 1988). The presence of PP, however, requires such analysis to be applied to sorted secondary peak trials alone (Fig. 1), which would introduce bias into the sample of selected interspike intervals. This type of analysis is further complicated by length bias sampling of interspike intervals during which the stimulus falls (i.e. a stimulus has a higher probability of occurring during a long interspike interval than during a short interspike interval) and by any serial correlation between consecutive interspike intervals. A graphical technique has therefore been used to determine the polarity of the post-synaptic potential, the contention being that if SP is caused by an excitatory post-synaptic potential then secondary peak discharges

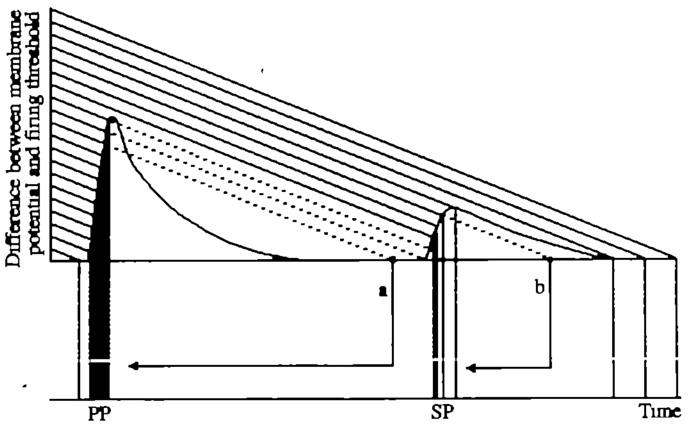

FIG. 9. Diagram of post-synaptic potentials following transcranial magnetic stimulation inferred from changes in firing probability The parallel oblique lines indicate the difference between the motor neuron's membrane potential and its firing threshold during the ramp phase of a series of membrane trajectories between voluntary discharges This difference tends towards zero at the intersection of these lines with the postulated sequence of excitatory post-synaptic potentials at various time-intervals during the course of an interspike interval. This causes the motor neuron to fire at the times indicated (peripheral conduction time is not shown). In the absence of the post-synaptic potentials the series of trajectories would have intersected a straight horizontal line, producing a uniform firing probability The effect of the excitatory post-synaptic potentials is to advance primary peak and secondary peak discharges from their expected times, as indicated by arrows a and b, respectively. The longer duration of SP when compared with PP is attributed to an excitatory post-synaptic potential of longer rise time. The amplitude of the excitatory post-synaptic potential underlying PP will influence the size of SP and its onset latency The period of zero firing probability following PP could also mask the effect of other post-synaptic potentials, including an inhibitory post-synaptic potential.

will occur earlier than expected and if by the decay of an inhibitory post-synaptic potential, then secondary peak discharges will be delayed. The effect on the interspike interval of magnetic stimuli when compared with simulated control stimuli suggests that both secondary peak and primary peak discharges occur earlier than expected (Fig. 6) and are thus due to excitatory post-synaptic potentials. A diagram of the proposed sequence of post-synaptic potentials produced in the spinal motor neuron by transcranial magnetic stimulation and their effect on firing probability is shown in Fig. 9. Additional events, however, including an inhibitory post-synaptic potential, are not excluded by present results.

The secondary rise in firing probability of human motor neurons which occurs after transcranial magnetic stimulation is therefore, we believe, due to the arrival at the motor neuron of a second phase of excitation transmitted over pathways which have both central and peripheral components. Likely candidates for this pathway are collateral activation of the gamma system by the descending volley and subsequent reflex motor neuron firing, or a long loop reflex initiated by activation of motor units other than that recorded in the muscle.

ACKNOWLEDGEMENTS

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REFERENCES

BONIFACE SJ, MILLS KR, SCHUBERT M (1991) Responses of single spinal motoneurons to magnetic brain stimulation in healthy subjects and patients with multiple sclerosis. *Brain*, **114**, 643–662.

BULLER NP, GARNETT R, STEPHENS JA (1980) The reflex responses of single motor units in human hand muscles following muscle afferent stimulation. *Journal of Physiology, London*, **303**, 337–349.

DAY BL, DRESSLER D, MAERTENS DE NOORDHOUT A, MARSDEN CD, NAKASHIMA K, ROTHWELL JC *et al.* (1989) Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology, London*, **412**, 449–473.

FETZ EE, GUSTAFSSON B (1983) Relation between shapes of post-synaptic potentials and changes in firing probability of cat motoneurones. *Journal of Physiology, London*, **341**, 387–410.

GANDEVIA SC, BURKE D (1988) Projection to the cerebral cortex from proximal and distal muscles in the human upper limb. *Brain*, **111**, 389–403.

GRIGG P, PRESTON JB (1971) Baboon flexor and extensor fusimotor neurons and their modulation by motor cortex. *Journal of Neurophysiology*, **34**, 428–437.

HESS CW, MILLS KR (1986) Low-threshold motor units in human hand muscles can be selectively activated by magnetic brain stimulation. *Journal of Physiology, London*, **380**, 62*P*.

HESS CW, MILLS KR, MURRAY NMF (1987*a*) Responses in small hand muscles from magnetic stimulation of the human brain. *Journal of Physiology, London*, **388**, 397–419.

HESS CW, MILLS KR, MURRAY NMF (1987*b*) Methodological considerations for magnetic brain stimulation. In: *Evoked Potentials III: The Third International Evoked Potentials Symposium*. Edited by C. Barber and T. Blum. Boston and London: Butterworths, pp. 456–461.

KNOX CK, POPPELE RE (1977) Correlation analysis of stimulus-evoked changes in excitability of spontaneously firing neurons. *Journal of Neurophysiology*, **40**, 616–625.

MARSDEN CD, MERTON PA, MORTON HB (1976) Stretch reflex and servo action in a variety of human muscles. *Journal of Physiology, London*, **259**, 531–560.

MILLS KR (1988) Excitatory and inhibitory effects on human spinal motoneurones from magnetic brain stimulation. *Neuroscience Letters*, **94**, 297–302.

MILLS KR, BONIFACE SJ, SCHUBERT M (1991) The firing probability of single motor units following transcranial magnetic stimulation in healthy subjects and patients with neurological disease. In: *Magnetic Motor Stimulation: Basic Principles and Clinical Experience. EEG and Clin. Neurophysiol. Suppl. 43*. Edited by W. J. Levy, R. Q. Cracco, A. T Barker and J. Rothwell. Elsevier, pp. 97–107.

PHILLIPS CG, PORTER R (1977) *Corticospinal Neurones: Their Role in Movement*. London: Academic Press.

POSER CM, PATY DW, SCHEINBERG L, MCDONALD WI, DAVIS FA, EBERS GC *et al.* (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, **13**, 227–231.

ROTHWELL, JC, GANDEVIA SC, BURKE D (1990) Activation of fusimotor neurones by motor cortical stimulation in human subjects. *Journal of Physiology, London*, **431**, 743–756.

STEPHENS JA, USHERWOOD TP, GARNETT R (1976) Technique for studying synaptic connections of single motoneurones in man *Nature, London*, **263**, 343–344.

TUCKWELL HC (1988) *Introduction to Theoretical Neurobiology*, Volume 2. *Nonlinear and Stochastic Theories*. Cambridge: Cambridge University Press, pp. 208–210.

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POTENTIALS EVOKED IN HUMAN AND MONKEY CEREBRAL CORTEX BY STIMULATION OF THE MEDIAN NERVE

A REVIEW OF SCALP AND INTRACRANIAL RECORDINGS

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SUMMARY

Somatosensory evoked potentials (SEPs) are generated in afferent pathways, subcortical structures and various regions of cerebellar and cerebral cortex by stimulation of somatic receptors or electrical stimulation of peripheral nerves. This review summarizes current knowledge of SEPs generated in cerebral cortex by stimulation of the median nerve, the most common form of stimulation for human research and clinical investigations. Major sources of data for the review are intracranial recordings obtained from patients during diagnostic or neurosurgical procedures, and similar recordings in monkeys.

Short-latency cortical SEPs in the 20–40 ms latency range consist of P20 and N30, recorded from motor cortex and frontal scalp; P25 and N35, recorded from cortex near the central sulcus and central scalp; and N20 and P30, recorded from somatosensory cortex and parietal scalp. Several lines of evidence including cortical surface and intracerebral recordings, neuromagnetic recordings and lesion studies in humans and monkeys, strongly support the conclusion that these potentials are generated in contralateral somatosensory cortex in areas 3b and 1, in contrast to the conclusion of many previous studies that SEPs recorded from the frontal scalp are generated in motor cortex and other frontal lobe areas. These potentials are primarily mediated by cutaneous afferents of the dorsal column-medial lemniscal system; the contribution of muscle afferents has not been completely resolved but appears to be small.

There is currently no evidence that short-latency SEPs are generated in cortex other than primary somatosensory cortex. Recordings from the vicinity of the second somatosensory area, from the supplementary motor and sensory areas and from surface cortex other than sensorimotor cortex have not detected reliable short-latency activity, although some of these regions generate long-latency potentials. Consequently, short-latency SEPs recorded from the scalp are similar to those recorded from the surface of sensorimotor cortex.

Old World monkeys such as *Macaca mulatta* and *M. fascicularis* provide an excellent model for human short-latency SEPs. All the potentials described above in humans have corresponding monkey analogues, with similar distributions over the cortical surface. The squirrel monkey, a New World species, exhibits the same potentials, but due to the different morphology of sensorimotor cortex, the surface distribution of SEPs is quite different.

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INTRODUCTION

Stimulation of a peripheral nerve evokes neuronal activity in many afferent tracts and nuclei of ascending somatosensory pathways and in various regions of cerebellar and cerebral cortex. A portion of this complex pattern of activity can be recorded in humans, either non-invasively from the scalp and body surface or intracranially during certain diagnostic or neurosurgical procedures. The purpose of this review is to assess our current understanding of potentials generated in cerebral cortex in response to stimulation of the median nerve, the most widely used stimulus both for clinical and research purposes. Most studies of cortical somatosensory evoked potentials (SEPs) have concentrated on activity thought to be generated in primary sensorimotor cortex. We will likewise focus on this region, with emphasis on cortical surface and intracerebral recordings obtained in humans and monkeys. Fewer recordings have been made from other cortical regions presumed to generate SEPs, for example the second somatosensory area (SII), but the available data will be reviewed briefly. The human intracranial recordings to be discussed here were obtained in patients being evaluated for possible surgical relief of intractable seizures (Spencer *et al.*, 1982) or to localize sensorimotor cortex prior to a cortical excision (Wood *et al.*, 1988); details of stimulating and recording conditions are given in Wood *et al.* (1988) and Allison *et al.* (1989*a*). Unless stated otherwise, all SEPs were evoked by stimulation of the contralateral median nerve at the wrist. Protocols for the recordings were approved by the Human Investigation Committees of the West Haven Veterans Administration Medical Center and Yale University School of Medicine. Recordings in monkeys, using techniques detailed in McCarthy *et al.* (1991), will also be discussed where they are helpful in clarifying the human data. The monkeys were treated in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

It is convenient to divide human cortical SEPs into 2 portions: short-latency potentials occurring within the first 40 ms after the median nerve stimulus, and long-latency potentials, occurring after 40 ms. This division is not entirely arbitrary, since as we shall see the short-latency potentials are mainly generated in a restricted region of somatosensory cortex contralateral to the median nerve stimulated and are minimally affected by anaesthetic and other intraoperative effects. In contrast, the long-latency potentials are generated in cortical regions in addition to somatosensory cortex, are generated by ipsilateral as well as by contralateral stimulation, and are more affected by recording conditions (e.g. Allison *et al.*, 1989*b*); these potentials will not be reviewed here.

SEPs GENERATED IN SENSORIMOTOR CORTEX

Human SEPs

After a sequence of subcortically generated components, short-latency SEPs recorded from the scalp typically have waveforms like those illustrated in Fig. 1. From frontal scalp a positivity in the 18–23 ms latency range is recorded. Following the polarity/latency nomenclature now used by most investigators, this potential will be labelled P20. Other potentials will be labelled in the same fashion. P20 is followed by a negativity of somewhat larger duration, N30. From parietal scalp a waveform of similar latency but of opposite polarity (N20 and P30) is recorded. These potentials will be referred to collectively as the 20 ms and 30 ms potentials.

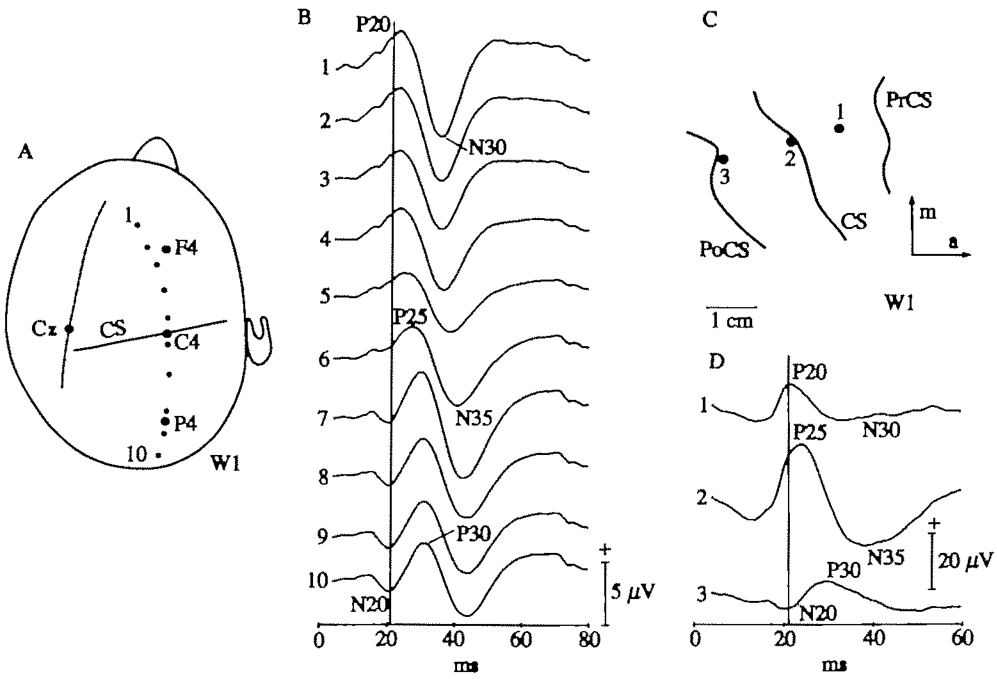

FIG 1. Short-latency SEPs recorded from the scalp and cortical surface. A, location of scalp electrodes in a patient under light sodium pentothal anaesthesia prior to a right hemisphere craniotomy. Drawing is an oblique view made from a photograph taken in surgery, and shows estimated location of midline (dashed line), scalp locations Cz, F4, C4 and P4, and central sulcus (CS). B, SEPs recorded to left median nerve stimulation from locations shown in A. C, cortical surface of the right hemisphere (a, anterior; m, medial) showing recording locations of SEPs shown in D. PoCS = postcentral sulcus; CS = central sulcus; PrCS = precentral sulcus D, SEPs recorded from the cortical surface. Patient was operated under general endotracheal anaesthesia (50% nitrous oxide and 0.5% isoflurane in oxygen) for Rasmussen's syndrome involving motor and premotor cortex. In B and D the isolatency line is at the approximate peak of N20 (21 ms) In this and following figures, SEPs were recorded with a bandpass of 1−1000 Hz (−3 dB); positive at the active electrode is upward, referenced to an ear (scalp recordings) or to temporal muscle near the craniotomy margin (cortical surface recordings); stimulus was delivered at 0 ms, stimulus artefact not shown, waveforms are the mean of 3−4 averages of 48−64 responses

From central scalp an intermediate waveform is recorded, consisting of a positivity, P25 (also called P22; *see* Fig. 3), peaking a few milliseconds later than P20, and followed by a negativity (N35) peaking a few milliseconds later than N30. In some recordings P25 is seen as a separate peak or as an inflection on the rising phase of P30, but in this example and in the general case P25 and P35 are not clearly separable from the precentral P20-N30 and postcentral N20-P30 potentials. Fig. 1D shows corresponding activity recorded directly from the cortical surface 2 h later, following a right hemisphere craniotomy. Similar potentials at about the same latencies are seen, but the transition from frontal to central to parietal waveforms, which occurs in the scalp recordings over a space of about 12 cm, occurs in the cortical surface recordings in a space of about 2 cm. The much better spatial resolution afforded by cortical surface recordings allows better determination of the locations of the generators of these SEPs.

The spatial distribution of potential over the scalp or cortical surface is better illustrated by isovoltage topographic maps. Fig. 2, *top*, shows scalp distributions at latencies corresponding to peaks of the 20 ms potentials, P25, and the 30 ms potentials. These maps show the average distribution across a group of 10 normal young adult subjects.

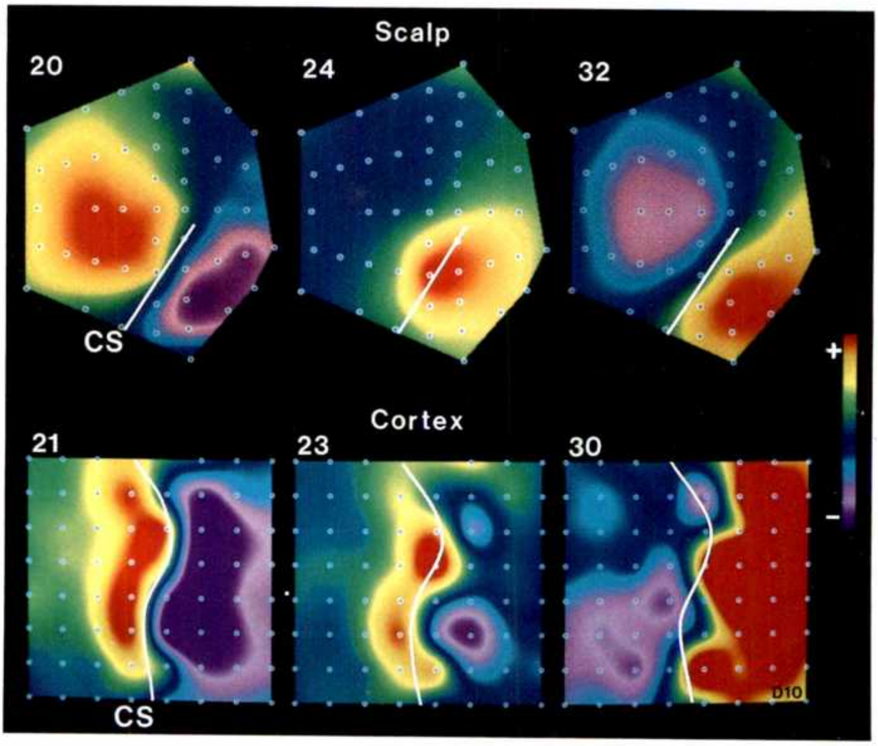

FIG. 2. Isovoltage contour maps. *Top*, distribution of potential over the scalp at the approximate peaks of the 20 ms potentials (20 ms), P25 (24 ms) and the 30 ms potentials (32 ms). These maps are averaged across 10 normal young adult subjects, using a 50 electrode montage of most 10−20 system locations and other locations as shown (white dots). Each map is a top view of the head, nose to the left, left ear at the bottom; bottommost and topmost locations are the left and right mastoids, respectively; anteriormost locations are the infraorbital bones; posteriormost location is O1; Cz is the midline location fourth from the left. The line indicates the approximate trajectory of the CS according to Jasper (1958) and Homan *et al.* (1987). *Bottom*, distribution of potentials over the cortical surface at the approximate peaks of the 20 ms potentials (21 ms), P25 (23 ms) and the 30 ms potentials (30 ms). The trajectory of the CS and electrode locations were determined from photographs made in surgery. The electrode array was an 8×8 grid with 5 mm spacing; each map thus represents an area 35×35 mm. Patient was operated under local anaesthesia, fentanyl and droperidol for a left frontal lobe tumour not involving sensorimotor cortex. In both sets of maps positive voltage is indicated by the green and red end of the colour scale, and negative voltage by the blue and violet end; each colour represents 1/16th the voltage from minimum to maximum at the latency depicted; voltage between electrode locations was estimated by linear interpolation.

The 20 ms and 30 ms potential fields are dipolar in shape and are broadly distributed with maxima and minima in the parietal and frontal regions. The major axis of the dipolar field is roughly orthogonal to the trajectory of the central sulcus (CS). At 24 ms the P25 distribution is seen as a region of positivity over the central scalp. Similar scalp topographies have been published by others (e.g. Goff *et al.*, 1977; Jones and Power, 1984; Deiber *et al.*, 1986; Tsuji and Murai, 1986; Desmedt *et al.*, 1987).

The distribution of voltage over the cortical surface for the same SEPs is shown for a single patient in Fig. 2, *bottom*, also at latencies corresponding to the peaks of the 20 ms potentials, P25, and the 30 ms potentials. At 21 ms the distribution shows a maximum over motor cortex corresponding to P20, and a minimum over somatosensory cortex (N20). At 23 ms P25 is seen as a region of positivity near the CS; in this case the peak of P25 is only 2 ms later than the peaks of P20 and N20, and the later part of that distribution is also apparent. The distribution at 29 ms is approximately the inverse of the one at 21 ms and exhibits a precentral minimum (N30) and postcentral maximum (P30). The scalp and cortical surface distributions are similar in shape but differ in spatial extent; the much greater spatial extent of the scalp distributions is a necessary consequence of the orientation of the generators and the greater distance of scalp electrodes from the active tissue (Goff *et al.*, 1978; Allison, 1982).

While some authors consider part of this activity to be generated in subcortical structures (e.g. Chiappa, 1983) the current consensus is that these potentials are of cortical origin. However, the specific cortical regions which generate them have been disputed. When discussing models of cortical electrogenesis it is helpful to recall that depolarization or hyperpolarization of a sheet of cortical pyramidal cells produces an extracellular potential field of one polarity at and distal to the apical dendrites, and of the opposite polarity at and proximal to the cell bodies (e.g. Landau, 1967; Schlag, 1973; Goff *et al.*, 1978). If the sheet of neurons is located in surface cortex ('radial' orientation) the dipolar potential field will have one polarity at the cortical surface and the opposite polarity as recorded from the lower layers of cortex and white matter, whereas neurons located in the wall of a sulcus ('tangential' orientation) produce a potential field of one polarity on one side of the sulcus and of the opposite polarity on the other side.

Papakostopoulos and Crow (1980) proposed that N20 was generated in somatosensory cortex, but that P20 was separately generated in motor or other precentral cortex. Desmedt and Cheron (1981) later extended this argument to the 30 ms potentials as well. This model, which may be termed a 'dual radial' model, is illustrated in Fig. 3A. Broughton (1969) concluded from intraoperative cortical surface recordings that the 20 ms and 30 ms potentials were produced by a tangential generator located in area 3b of somatosensory cortex, which in humans and Old World primates is located in the posterior wall of the CS (Vogt, 1928; Powell and Mountcastle, 1959*a*). This will be referred to as the 'tangential' model (Fig. 3B). Most investigators agree that these models alone cannot account for all the features of SEPs recorded from the scalp or from the cortical surface and that a radial generator is needed to account for (at least) P25 or P22. The model proposed by Allison *et al.* (1980, 1989*a*) places the radial generator in area 1 of somatosensory cortex (the 'tangential + somatosensory radial' model; Fig. 3C), whereas the model proposed by Deiber *et al.* (1986) and Desmedt *et al.* (1987) (*see also* Cohen and Starr, 1987; Nogueira *et al.*, 1989; Abbruzzese *et al.*, 1990) places it in motor cortex (the 'tangential + motor radial' model; Fig. 3D).

Comparison of SEPs in humans and Old World monkeys

Before discussing the models illustrated in Fig. 3 it will be helpful to compare SEPs recorded in humans and in Old World monkeys, since some predictions of these models can be tested best in monkey recordings.

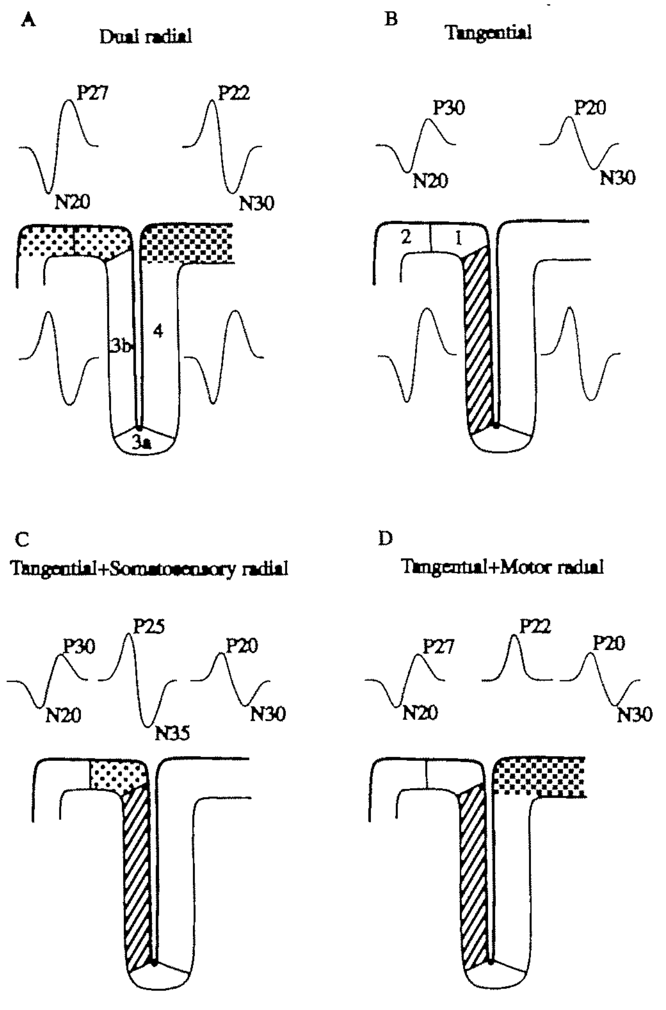

FIG. 3. Schematic representation of alternative hypotheses of the origin of short-latency human SEPs. A, predicted waveforms produced by excitation of neurons located in motor and somatosensory cortex In this model the nomenclature (Desmedt and Cheron, 1981) emphasizes differences in peak latency of the precentral and postcentral potentials B, predicted waveforms produced by excitation of neurons in area 3b in the posterior wall of the CS. In this model the nomenclature (Allison *et al* , 1980) emphasizes similarities in latency of the precentral and postcentral potentials. Models A and B deal specifically with the 20 ms and 30 ms potentials; in each drawing the upper waveforms are those recorded from the cortical surface, and the lower waveforms are those predicted by the model to be recorded in white matter underneath somatosensory or motor cortex C, this model adds a radial generator in area 1 of somatosensory cortex to the tangential generator in area 3b, in order to account for P25-N35 as recorded from the scalp or cortical surface. D, this model adds a radial generator in motor cortex (area 4) to the tangential generator in area 3b, to account for P22 recorded from the scalp To simplify the drawings in C and D, only waveforms recorded from the cortical surface are illustrated.

Fig. 4 illustrates short-latency SEPs recorded from the surface of the hand representation of sensorimotor cortex of humans and monkeys. The 3 waveforms characteristically seen in human cortical surface recordings (Fig. 1) are also illustrated

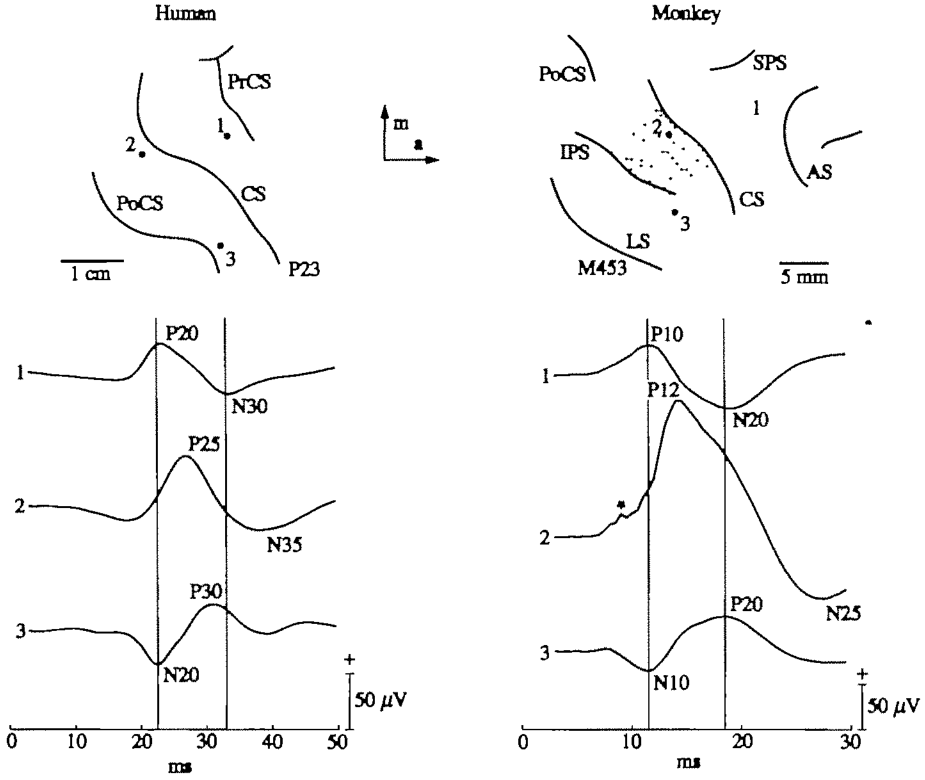

FIG. 4. Comparison of short-latency SEPs in monkeys and humans. *Human*, cortical surface recordings from right sensorimotor cortex (*upper drawing*). Patient was operated under light general anaesthesia (10% nitrous oxide and 0.1% isoflurane in oxygen, supplemented with fentanyl and droperidol) for excision of a frontal lobe epileptogenic focus not involving sensorimotor cortex. Isolatency lines are at the approximate peaks of P20 and N20 (22 ms), and N30 and P30 (32 ms). *Monkey*, cortical surface recordings from right sensorimotor cortex (*upper drawing*) of a cynomolgus monkey (*Macaca fascicularis*) under light sodium pentothal anaesthesia The stippled area indicates the hand representation of somatosensory cortex as determined by single-unit or multi-unit recordings in anaesthetized and unanaesthetized *M. mulatta* and *M fascicularis* (McKenna *et al.*, 1982; Pons *et al.*, 1985). AS = arcuate sulcus; CS = central sulcus; IPS = intraparietal sulcus; LS = lateral sulcus; PoCS = postcentral sulcus; SPS = superior precentral sulcus Of the total hand area approximately the lateral two-thirds is devoted to the median nerve representation (digits 1–3). Isolatency lines are at the approximate peak of P10 and N10 (11.5 ms), and N20 and P20 (18 5 ms). Stimulating and recording conditions for this and following monkey recordings were the same as for the human recordings except that the reference electrode was in bone over the frontal sinus Adapted from McCarthy *et al.* (1991).

here: P20-N30 is the largest in the hand area of motor cortex ('precentral', location 1); P25-N35 is largest in the medial portion of the hand area of somatosensory cortex near the CS but is also recorded with smaller amplitude from motor cortex near the CS ('pericentral', location 2); and N20-P30 is largest in the lateral portion of the hand area of somatosensory cortex and adjacent parietal cortex ('postcentral', location 3). In the monkey, P10-N20 is largest in the hand area of motor cortex (location 1), P12-N25 is largest in the medial portion of the hand area of somatosensory cortex near the CS (location 2), and N10-P20 is largest in the lateral portion of the hand area of somatosensory cortex and adjacent parietal cortex (location 3). A small positivity at about 7 ms (location 2, asterisk) reflects subcortical activity, primarily the thalamocortical afferent volley (Arezzo *et al.*, 1979). The similarity of the monkey and human waveforms and relative latencies is clear, although absolute latencies in monkeys are approximately 10 ms shorter due to the shorter conduction pathway. We conclude, in agreement with Arezzo *et al.* (1981), that the monkey and human potentials reflect the same neuronal activity and correspond as follows:

	Monkey	*Human*
Precentral	P10	P20
	N20	N30
Peri-CS	P12	P25
	N25	N35
Postcentral	N10	N20
	P20	P30

In the following sections we will regard these human and monkey SEPs as being equivalent.

Intracranial recordings of the human 20 ms and 30 ms SEPs and their monkey analogues

Scalp and cortical surface recordings alone cannot decide between the dual radial and tangential models, since both models make similar predictions regarding potentials recorded from the cortical surface or scalp. However, the 2 models make quite different predictions about the intracerebral distribution of potential. The dual radial model predicts inversions of polarity of the surface potentials when recorded from underlying white matter or other intracerebral locations (Fig. 3A). (We should note that this prediction has not been made explicitly by proponents of the dual radial model, but it follows from the premise that the potentials are generated in surface cortex of the frontal and parietal lobes.) By contrast, the tangential model predicts that the precentral and postcentral potentials will not show polarity inversion from surface to depth but rather should be recorded with the same polarity as the surface recordings but with decreasing amplitude as a function of distance from the CS. Recordings relevant to these predictions can be summarized as follows:

(1) At precentral intracerebral locations recorded with depth probes, including premotor cortex and frontal mesial cortex, precentral P20 and N30 were recorded which are similar in amplitude, waveform and polarity to potentials recorded from the scalp, but were smaller than the potentials recorded from the surface of motor cortex adjacent to the CS (Allison *et al.*, 1989*a*; *see also* Yamada *et al.*, 1984).

(2) P20 and N30 do not invert in polarity from the surface to white matter of precentral cortex, as determined by depth probe recordings anterior to motor cortex (Allison *et al.*, 1989*a*). Instead, in depth probe recordings the largest precentral potentials are recorded about 1 cm below the cortical surface, as would be predicted if the potentials were generated in a wall of the CS. The human CS is about 1.8 cm deep (our measurements of 6 hemispheres), and area 3b occupies most of its posterior bank. The major axis of a dipolar generator located in area 3b would thus be about 1 cm beneath the cortical surface.

(3) The dual radial model predicts that the largest P20 and N30 should be recorded from the surface of motor cortex, whereas the tangential model predicts that they should be recorded largest from the surface of area 3b. In a patient in whom the hand area of motor cortex was completely excised, the amplitude of P20 and N30 was about 3 times larger when recorded from the exposed anterior wall of the postcentral gyrus than when recorded from the surface of motor cortex prior to the excision (Allison *et al.*, 1991). Similar recordings were also made in cynomolgus monkeys (McCarthy *et al.*, 1991). These recordings confirm this prediction of the tangential model, and disconfirm the dual radial model, since the human P20 and N30 and the monkey P10 and N20 were recorded in the absence of motor cortex.

(4) N20 and P30 do not show inversion of polarity in transcortical recordings from the surface and white matter of somatosensory cortex, and smaller versions of these potentials are recorded from the surface of the parietal lobe and from postcentral depth probe locations (Allison *et al.*, 1989*a*).

These observations support the tangential model of Fig. 3B.

Relative latency and amplitude of precentral and postcentral SEPs

A spatially fixed, time-varying point dipole in a homogeneous volume conductor produces positive and negative potentials which are symmetric in space and time. In contrast, the 20 ms and 30 ms potentials often show both amplitude and latency disparities as recorded from the precentral and postcentral regions of scalp or cortical surface. These deviations from symmetry are the most common objection to the tangential model (Desmedt and Cheron, 1980, 1981; Papakostopoulos and Crow, 1980, 1984; Kimura and Yamada, 1982; Lueders *et al.*, 1983; Maccabee *et al.*, 1983; Mauguière *et al.*, 1983*a,b*; Yamada *et al.*, 1984; Desmedt and Bourguet, 1985; De Weerd *et al.*, 1985; Deiber *et al.*, 1986; Slimp *et al.*, 1986). We believe that such objections are unfounded for empirical and theoretical reasons discussed in this section.

Relative latency. The peak latencies of the precentral P20 and N30 are often 1 – 3 ms later than those of the postcentral N20 and P30. This is true both for scalp (e.g. Sidman *et al.*, 1978; Desmedt and Cheron, 1980; Wood, 1982; Maccabee *et al.*, 1983; Yamada *et al.*, 1984) and cortical surface (Papakostopoulos and Crow, 1980, 1984; Broughton *et al.*, 1981; Wood *et al.*, 1988; Allison *et al.*, 1989*a*) recordings. In Fig. 1B, for example, the peak of P20 is about 1 ms later than the peak of N20, and N30 is about 3 ms later than P30. These latency differences have been regarded as invalidating the tangential model on the assumption that potentials on either side of a dipole necessarily have the same peak latency (Desmedt and Cheron, 1980; Papakostopoulos and Crow, 1980, 1984; Kimura and Yamada, 1982; Maccabee *et al.*, 1983; Yamada *et al.*, 1984; De Weerd *et al.*, 1985).

Evoked potentials have been studied extensively in animals and provide the best available data regarding the properties of potential fields generated by synchronously activated groups of neurons. Evoked potentials generated in cerebral cortex show an inversion of polarity as an electrode is lowered from the surface to underlying white matter (Schlag, 1973), that is, a change of polarity is recorded as an electrode passes from the region of positive (source current) to negative (sink current) voltage. An inversion of polarity of large amplitude focal potentials thus provides strong evidence for the presence of a local generator with dipolar properties (Amassian *et al.*, 1964; Kelly *et al.*, 1965; Towe, 1966; Schlag, 1973; Creutzfeldt and Houchin, 1974; Llinás and Nicholson, 1974; Wood and Allison, 1981). Representative examples of potential fields in which the latencies of potentials from the two sides of a dipolar generator differ significantly, may be summarized as follows: in cat superior olivary complex the excitation of neurons of the medial segment by click stimuli evoked a spatially symmetric dipolar field; the peak latency of the positive field was about 1.2 ms later than the corresponding negativity (Freeman, 1975). In frog cerebellum, depolarization of Purkinje cell dendrites by local cortical stimulation produced a dipolar field in which the positive source potential in the region of the cell body was about 0.4 ms later than the peak of the negativity in the dendritic region (Llinás and Nicholson, 1974). Depolarization of granule cells in cat and rabbit olfactory bulb by olfactory nerve stimulation produced a surface-negative, deep-positive field in which the positivity was about 2 ms later than the negativity in some recordings, while similar latencies were seen in other recordings (Freeman, 1972). In cat visual cortex the surface primary positivity evoked by optic nerve stimulation was 0.4 ms later than the deep negativity, whereas the following surface primary negativity peaked about 1.5 ms earlier than the white matter positivity (Mitzdorf and Singer, 1980). In cat somatosensory cortex the primary positivity evoked by thalamic or peripheral stimulation peaked about 0.8 ms later than the depth negativity (Perl and Whitlock, 1955), or was similar in latency (Amassian *et al.*, 1964). In rhesus monkey somatosensory cortex the primary positivity evoked by median nerve stimulation was either earlier or later than the white matter negativity depending on electrode location; the latency differences were thought to be partly spurious due to the superposition of potentials generated nearby (Arezzo *et al.*, 1979, 1981). In squirrel monkey somatosensory cortex the surface primary potentials evoked by median nerve stimulation was 2–5 ms different in peak latency than the corresponding deep potentials (*see* Fig. 12).

This sampling of results shows that asymmetry in latency of the positive and negative portions of neuronally generated dipolar fields is the rule rather than the exception. Because the pyramidal cells of cerebral cortex are not activated simultaneously by an afferent volley, but sequentially from layers 3–4 to more superficial layers (Towe, 1966; Schlag, 1973) it might be supposed that this pattern of activation could produce latency differences in the two halves of the dipolar field. However, the latency differences in the positive and negative fields generated in the medial segment of the superior olivary complex suggest that this cannot provide a general explanation. This structure is composed of a monolayer of neurons which are activated simultaneously by clicks (Freeman, 1975), and thus provides the simplest possible example of a neuronal dipolar generator, yet the positive source potential peaks about 2 ms later than the negative sink potential. There is a tendency in the animal recordings for the source positivity to peak 0.5–2.0 ms later than the corresponding negative sink whether the sinks are in dendrites (Freeman, 1972, 1975; Llinás and Nicholson, 1974) or near cell bodies (most other studies reviewed). Thus, these recordings show that excitation of a discrete neuronal population produces dipolar fields which can be asymmetric in peak latency by an amount comparable with that seen in the human 20 ms and 30 ms potentials.

Although precentral peak latencies are often later than postcentral latencies, the converse is sometimes seen. Fig. 5 shows 3 recordings in which the precentral P20 and N30 peak latencies were earlier than the postcentral N20 and P30 peak latencies, respectively

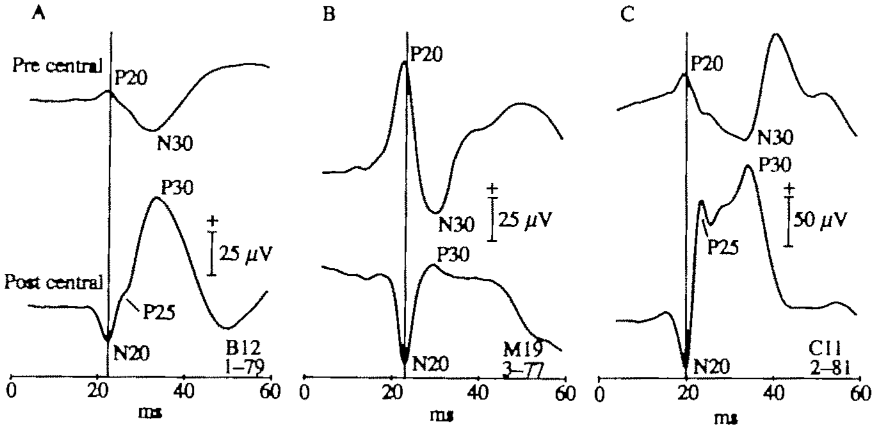

FIG. 5. Relative latencies of precentral and postcentral potentials. Precentral (*top*) and postcentral (*bottom*) traces are averages across all cortical surface locations from which large-amplitude 20 ms and 30 ms potentials were recorded. A, average of 4 precentral and 4 postcentral waveforms. Patient was operated under local anaesthesia and fentanyl for excision of a left frontal lobe epileptogenic focus not involving sensorimotor cortex. B, average of 5 precentral and 4 postcentral waveforms; patient was operated under local anaesthesia, fentanyl and droperidol for a right frontal lobe epileptogenic focus not involving sensorimotor cortex. C, average of 9 precentral and 9 postcentral waveforms. Patient was operated under light general anaesthesia (10% nitrous oxide in oxygen with fentanyl and supplemental muscle relaxant) for excision of a left parieto-occipital tumour not involving sensorimotor cortex. In each case the isolatency line is at the peak of N20.

(these results are seen in about 20% of cortical surface recordings). The waveforms labelled Precentral and Postcentral are the mean P20-N30 and N20-P30 waveforms recorded, respectively, from all precentral and postcentral cortical surface locations; this procedure avoids bias in selecting particular waveforms for comparison. One version of the dual radial model supposes that P20 and N30 are generated by afferent input to motor cortex relayed via somatosensory cortex (Desmedt and Cheron, 1980). This hypothesis requires that precentral latencies be later by at least the time required for intracortical transmission from somatosensory to motor cortex. The hypothesis is necessarily incorrect when precentral latencies are earlier than (Fig. 5) or equal to (e.g. Fig. 1D) postcentral latencies. In addition, human transcortical recordings (Stohr and Goldring, 1969; Goldring *et al.*, 1970; Allison *et al.*, 1989*a*) provide no evidence that area 2 (the only region of somatosensory cortex that projects to area 4; Jones, 1983) generates recordable short-latency potentials. It therefore seems unlikely that area 2 could serve as a short-latency relay for the potentials recorded from motor cortex.

Relative amplitude. Several factors may produce amplitude inequalities in neuronal dipolar fields, even in a homogeneous volume conductor. For example, at the cellular level asymmetries can arise if the depolarized region is smaller (and current density correspondingly higher) than the cellular regions providing source current (Bantli, 1974; Llinás and Nicholson, 1974). If the dipole axis is not tangential to the surface, the upward-pointing side of the field will be recorded at larger amplitude at the surface than the downward-pointing field (Cohen and Cuffin, 1983). In the human brains we have examined the posterior wall of the CS is tilted in either direction and hence could produce amplitude asymmetries in either direction.

Another relevant factor is the morphology of the postcentral gyrus, which is often curved in the hand area with the convexity facing anteriorly and the concavity facing posteriorly (Wood *et al.*, 1988; and *see* Fig. 1c). The effect of curvature is to increase potential amplitude in the concavity and to decrease it over the convexity; this phenomenon has been observed in potentials generated in hippocampus, olfactory bulb and other curved surfaces (Bantli, 1974; Freeman, 1975; Klee and Rall, 1977). The amplitude asymmetry in Purkinje cell dipolar fields can be accounted for by taking into account the curvature of the cerebellar surface (Bantli, 1974). Assuming that the region of area 3b activated by median nerve stimulation is formed as illustrated in Fig. 6, it can be calculated from Table I of Klee and Rall (1977) that the precentral (convexity) potentials should be approximately 40% of the amplitude of the postcentral (concavity) potentials if both are recorded at the same distance from the CS. In 6 patients in whom the morphology of the hand area approximated the model of Fig. 6 and the precentral and postcentral potentials could be determined accurately, the mean value was 51%. Conversely, in other patients there is little or no detectable bend in the CS in the hand area; in such patients amplitudes tend to be symmetric across the CS (*see* Allison, 1982, fig. 1; Wood *et al.*, 1988, fig. 1). These considerations show that objections to the tangential model on grounds of latency and amplitude disparity between the precentral and postcentral potentials are unfounded.

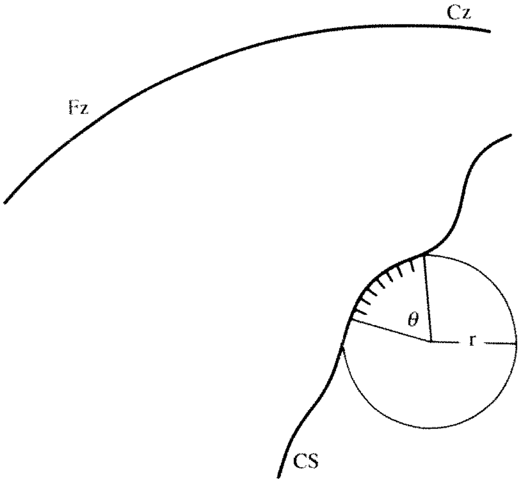

FIG. 6. Schematic drawing of the left hemisphere showing the frontomedially directed bend of the CS in the hand area; in such cases somatosensory cortex forms a convex cap of tissue with a radius (r) of 13 ± 4 mm (mean ± SD of 16 cases). The angle θ subtended by the cortex activated by median nerve stimulation is unknown, but judging by the region of large-amplitude postcentral potentials is estimated to be of the order of 70°.

Scalp and cortical surface recordings of P25 and N35

In addition to the 20 ms and 30 ms potentials, a central scalp positivity (P25) in the 22–26 ms latency range can often be recorded, followed by a negativity (N35) in the 32–40 ms range (Figs 1–4). P25 corresponds to the P22 of Deiber *et al.* (1986) and Desmedt *et al.* (1987), to the P2 in some recordings of Lueders *et al.* (1983), and to the P23 of Tsuji and Murai (1986). From central scalp it can sometimes be recorded as a more or less separate peak. Note in Fig. 1B, however, that the positivity labelled

P25 gradually decreases in latency anteriorly to become the positivity labelled P20, and merges posteriorly with P30. That is, in scalp recordings P25 is not recorded in isolation but rather is mixed in varying degrees with the 20 ms and 30 ms potentials. This and other problems in the identification and measurement of this activity have led to uncertainty as to its origin.

Intracranial recordings allow P25 and N35 to be recorded in relative isolation and have resolved much of this uncertainty. P25 and its monkey analogue P12 are recorded at large amplitude from a small region in the medial portion of the hand area of somatosensory cortex near the CS (Figs 1D, 4; *see also* Figs 10, 11), and in some recordings from motor cortex near the CS (Fig. 2, at 24 ms and 23 ms; *see also* Wood *et al.*, 1988; Allison *et al.*, 1989*a*). Transcortical recordings by Goldring *et al.* (Stohr and Goldring, 1969; Goldring *et al.*, 1970) demonstrate that these potentials are primarily generated in the anterior portion of the crown of somatosensory cortex. In some patients similar (but usually smaller and slightly later) potentials may be generated in the posterior portion of the crown of motor cortex in area 4. The similarity of the potentials recorded transcortically by Goldring *et al.* with P25 and N35 is shown in Fig. 7, demonstrating that the potentials recorded by the two groups are equivalent.

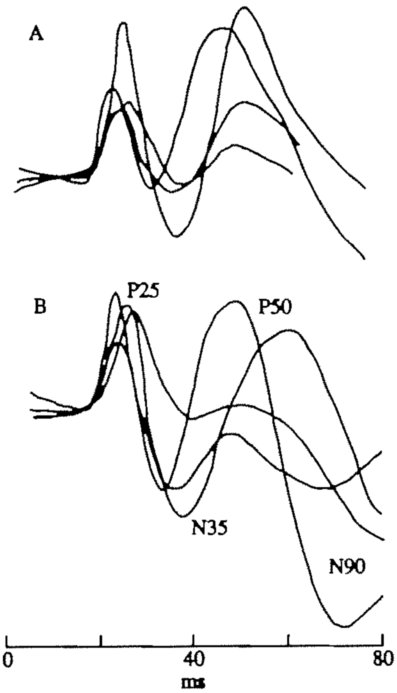

Fig. 7 A, potentials recorded transcortically from the hand area of somatosensory cortex of 4 patients. Redrawn from Stohr and Goldring (1969), figs 1E and 2D, and from Goldring *et al.* (1970), fig. 10 JW and CK. B, potentials recorded from the medial anterior portion of the hand area of somatosensory cortex in 4 patients of Wood *et al.* (1988) and Allison *et al.* (1989*a*). In both sets of recordings 3 of the 4 patients were operated under local anaesthesia Amplitudes are not plotted to the same scale; in A P25-N35 peak-to-peak amplitudes ranged from 80 to 210 μV, and in B from 60 to 135 μV

In some cases, P25-like potentials in the 28−38 ms latency range can be recorded (Allison *et al.*, 1989*a*). These potentials have spatial distributions similar to that of P25 except that they are largest over the central and lateral portion of the hand area of somatosensory cortex. It is likely that these potentials are also generated in area 1. P25 and the later P25-like potentials may reflect the patchy activation of discrete regions of area 1 demonstrated by 2 deoxyglucose-labelling studies of monkey somatosensory cortex (Juliano and Whitsel, 1985).

Magnetic recordings from somatosensory cortex

The magnetoencephalogram (MEG) provides another method of determining neuronal generator locations and orientations (for reviews *see* Williamson and Kaufman, 1981; Cohen and Cuffin, 1983). MEG recordings from sites overlying sensorimotor cortex to contralateral median nerve or digit stimulation, reveal a robust tangential source located 2−3 cm below the scalp in the somatotopically appropriate region of somatosensory cortex (Williamson and Kaufman, 1981; Hari *et al.*, 1984; Okada *et al.*, 1984). In these studies 20 ms and/or 30 ms magnetic fields were described which correspond to the 20 ms and 30 ms potentials. Cohen and Cuffin (1983) and Wood *et al.* (1985) recorded MEGs and SEPs in the same subjects. Fig. 8 shows electric and magnetic maps at 21 ms (at the peaks of the 20 ms potentials) for one of their subjects. The potential map (Fig. 8A) is similar to those of Fig. 2 at 20 ms and 21 ms and illustrates the P20 precentral maximum and the N20 postcentral minimum, with a zero-potential line approximately over the CS. The magnetic map (Fig. 8B) is centred over the same region but differs in orienation by 88°; the predicted value is 90°, assuming that all current flow and magnetic flux is due to a single tangential generator. The electrical and magnetic results considered separately can be explained by a single tangential generator, or by separate

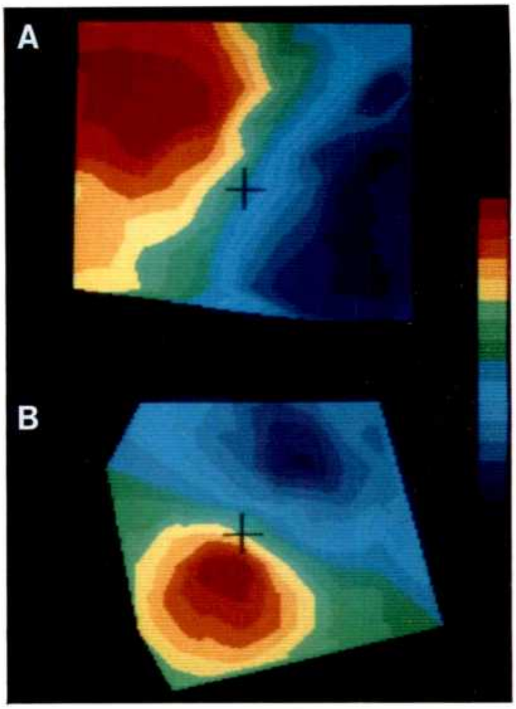

FIG. 8. Comparison of isopotential (A) and isofield (B) contour maps at the peak of P20 and N20 (21 ms). Recordings during quiet waking from the left hemisphere of a normal young adult subject. The left side of the map is toward the nose and the bottom toward the left ear; scalp location C3 is indicated by the cross. The red end of the colour scale indicates positive voltage (A) and flux flowing out of the head (B). Each colour represents 1/16th of the difference between maximum and minimum voltage or flux. Adapted from Wood *et al.* (1985).

radial generators in motor and somatosensory cortex. However, both sets of results can only be explained by a single tangential generator (Wood *et al.*, 1985). The direction of intracellular current flow detected in magnetic recordings is consistent with initial depolarization of neurons in somatosensory cortex but not in motor cortex.

In adult humans the scalp and skull is about 1.5 cm thick, and the CS is on average 1.8 cm (our measurements) or 2 cm (Delmas and Pertuiset, 1959) deep. The centre of area 3b is thus about 2.5 cm below the scalp. Wood *et al.* (1985) concluded that the 20 ms and 30 ms electric and magnetic fields were well accounted for by a tangential generator located in somatosensory cortex about 2.5–3.0 cm below the scalp. While the electric and magnetic recordings do not rule out the possibility of additional radial generators (to which the MEG is insensitive), they demonstrate that area 3b is the major contributor to the 20 ms and 30 ms potentials.

Lesions of somatosensory or motor cortex

Lesions of somatosensory or motor cortex provide another test of the models of Fig. 3. The dual radial model predicts that the postcentral and precentral generators will be differentially affected by lesion of motor and somatosensory cortex, respectively, whereas the tangential model predicts that both precentral and postcentral potentials will be affected by somatosensory cortex lesions but unaffected by motor cortex lesions. The tangential + somatosensory radial model predicts that lesions of somatosensory cortex will decrease or abolish all potentials, whereas the tangential + motor radial model predicts that P22 (P25) will survive lesions of somatosensory cortex but be reduced or abolished by lesions of motor cortex.

Conflicting results have been reported. Several groups concluded that human precentral and postcentral potential amplitudes were differentially affected by frontal and parietal lesions, respectively, and interpreted this as supporting the dual radial model (Mauguière *et al.*, 1983*a*; De Weerd *et al.*, 1985; Slimp *et al.*, 1986). However, Tsuji and Murai (1986) reported normal SEPs (except for a reduction in what they labelled N30) in patients with complete hemiplegia but normal sensation, indicating a lesion limited to motor cortex. They also reported the absence of SEPs in patients with complete hemiplegia and sensory loss. These authors interpreted their results as favouring the tangential model. A problem in studies of naturally occurring lesions is that patients were not studied prior to their illness. The amplitude asymmetry of precentral and postcentral potentials can be substantial, as illustrated in Fig. 9. In this patient the small potentials recorded from the left frontal scalp, compared with the large potentials recorded from the left parietal scalp (Fig. 9, RMN), might suggest a left frontal abnormality. On the other hand, the small potentials recorded from the right parietal scalp compared with the large potentials recorded from the right frontal scalp (Fig. 9, LMN), might suggest a right parietal abnormality. In fact the patient had a large left parietal sarcoid which was resected a week after these recordings. In our experience, similar large asymmetries apparently unrelated to pathology are common. For example, in the neurologically normal young adults whose scalp topographies were summarized in Fig. 2, *top*, the between-subject ratio of peak-to-peak precentral (P20-N30) to postcentral (N20-P30) amplitudes ranged from 0.54 to 2.36 for the left hemisphere (to right median nerve stimulation), and from 0.80 to 4.94 for the right hemisphere (to left median nerve stimulation). That is, precentral amplitudes ranged from half as large to almost 5 times as large as postcentral amplitudes.

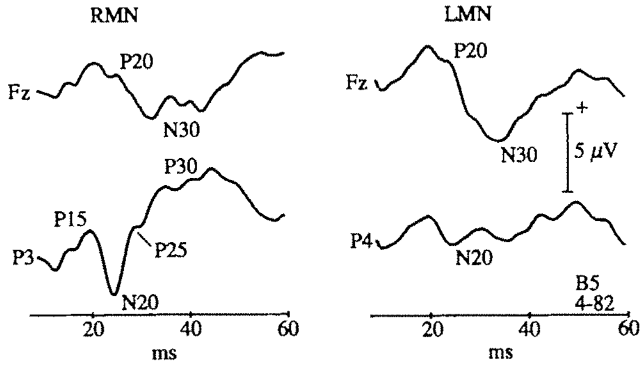

FIG 9. Scalp recordings during quiet waking from the left hemisphere to right median nerve (RMN) stimulation, and from the right hemisphere to left median nerve (LMN) stimulation. In both sets of recordings the largest potentials were recorded at the locations shown

Within-subject variability was also large; the largest variation in ratio was 0.79−1.7. That is, in this subject precentral potentials were about 20% smaller than postcentral potentials in one hemisphere, but were 70% larger in the other hemisphere. Given this large between- and within-subject variability, conclusions about abnormality based on comparisons of precentral and postcentral amplitudes cannot be made with confidence in the absence of pre-lesion recordings from the affected hemisphere.

Surgical removal of somatosensory or motor cortex, with SEP recordings before and after removal, provides a better test of the two models. In a patient studied by Allison *et al.* (1991), excision of the hand area of somatosensory cortex abolished all SEPs including the 20 ms and 30 ms potentials, both in cortical surface recordings and in later scalp recordings; normal potentials were recorded prior to the excision. Conversely, in another patient the 20 ms and 30 ms potentials could still be recorded following complete removal of the hand area of motor cortex. Similar results have been obtained in monkeys; removal of the hand area of somatosensory cortex abolished all cortical potentials precentrally as well as postcentrally (Fig. 10). In contrast, all potentials remained following removal of motor cortex (Fig. 11). Removal of areas 1 and 2 in the crown of somatosensory cortex greatly reduced the amplitude of P12-N25 (the monkey analogues of the human P25-N35) while leaving the 10 ms and 20 ms potentials relatively unaffected (Allison *et al.*, 1991). These results are inconsistent with the dual radial model and the tangential+motor radial model but provide strong support for the tangential model and the tangential+somatosensory radial model.

SEPs in New World monkeys

In Old World monkeys (such as the cynomolgus monkey) and humans, area 3b is enfolded in the posterior wall of the CS (Vogt, 1928; Powell and Mountcastle, 1959*a*) and is thought to be homologous to primary somatosensory cortex (SI) of other mammals (Kaas *et al.*, 1981). According to the tangential model the orientation of area 3b neurons parallel to surface cortex and scalp accounts for the anterior-posterior orientation of the 20 ms and 30 ms potential fields. It is not possible to manipulate this orientation

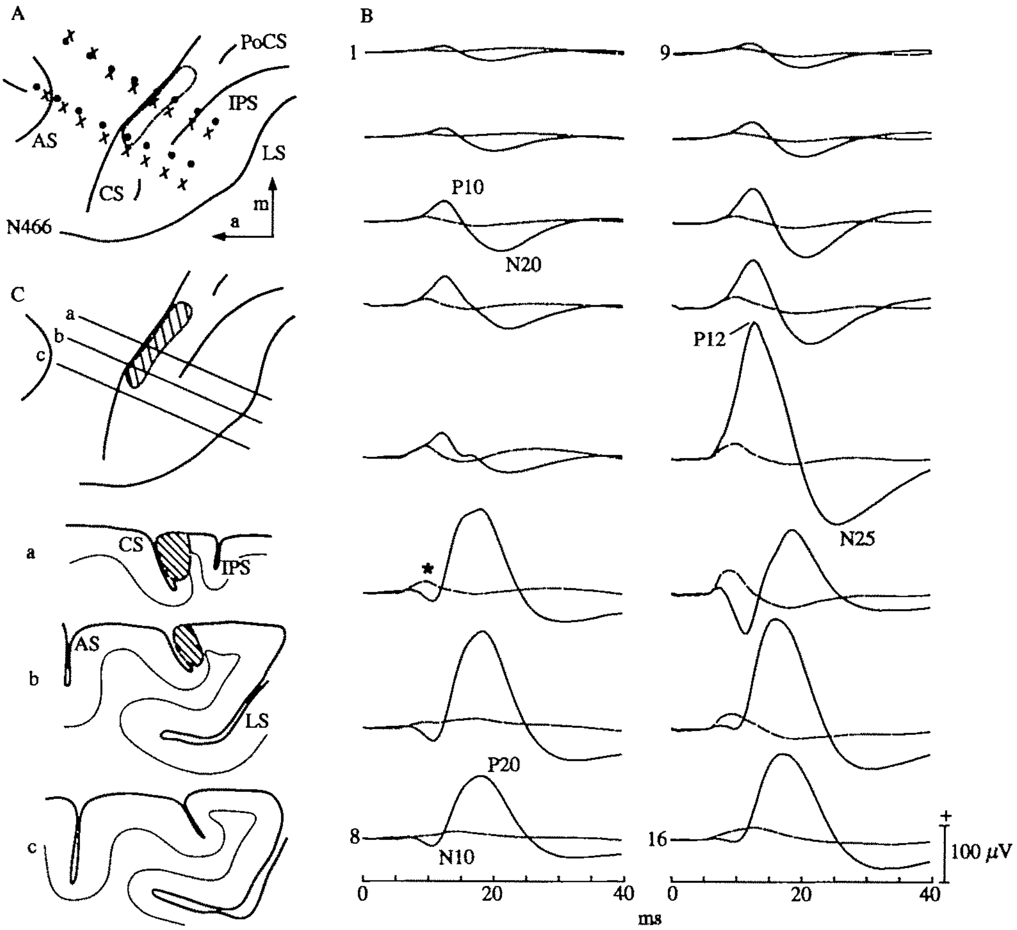

FIG. 10. Effects on SEPs of partial removal of monkey somatosensory cortex. A, locations of left hemisphere cortical surface electrodes before (solid circles) and after (crosses) removal of the anterior wall of the postcentral gyrus and the overlying portion of the crown (dashed line) B, cortical surface recordings under moderate sodium pentothal anaesthesia before (solid traces) and after (dashed traces) the lesion Following the lesion only the subcortical positivity at 7 ms (e.g location 6, asterisk) remained C, reconstruction of the lesion. Adapted from Allison *et al.* (1991).

directly to determine topographic effects. However, a natural experiment can be performed. In the squirrel monkey, a New World primate, the hand area of somatosensory cortex is lateral to the shallow CS and area 3b is not enfolded; thus in this species anterior-posterior inversions of polarity should not be seen. Instead, a surface positive-negative sequence should be recorded both from areas 3b and 1, with polarity inversion from surface to white matter in both areas. The area 3b potentials would be expected to exhibit peak latencies a few milliseconds earlier than the area 1 potentials, corresponding to the latency differences between the human P20 and P25, and between N30 and N35.

The recordings of Fig. 12 support these predictions. Figure 12A summarizes the results

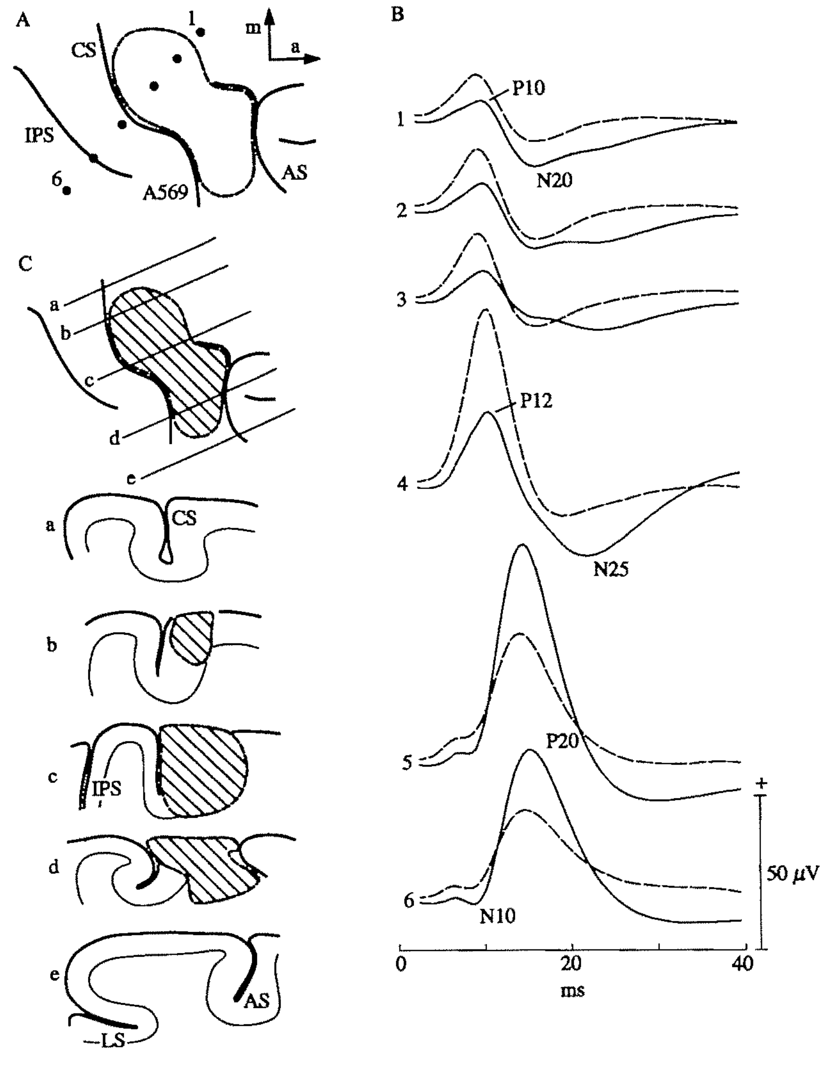

FIG. 11. Effects on SEPs of removal of the hand area of monkey motor cortex. A, locations of right hemisphere epidural electrodes (solid circles) and lesion (dashed line). B, epidural recordings under light sodium pentothal anaesthesia before (solid traces) and after (dashed traces) the lesion. C, reconstruction of the lesion. Adapted from Allison *et al.* (1991).

of Zimmerman (1968) and Dykes (1978), who recorded SEPs evoked by finger stimulation. Two separate responsive regions were found, which when superimposed on the cytoarchitectonic map of Sanides (1968) are seen to be located primarily in areas 3b and 1. In Zimmerman's recordings the peak latencies of the area 3b potentials were 3–7 ms earlier than the area 1 potentials. Recording sites outside these regions showed smaller amplitude potentials of the same polarity. We have confirmed these results in 5 squirrel monkeys; in addition, transcortical recordings showed inversions of polarity from surface to white matter in both areas 3b and 1 (Fig. 12B). Peak latencies of the

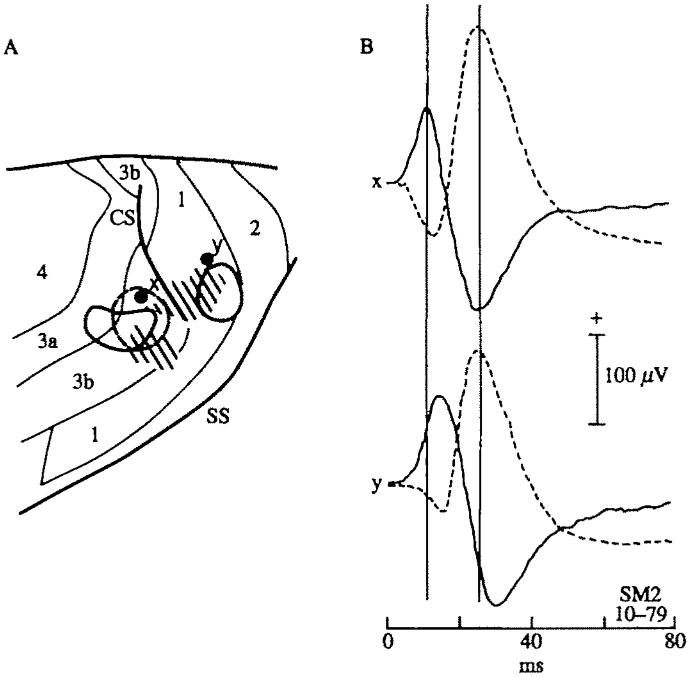

FIG. 12. SEPs in squirrel monkeys. A, region from which largest amplitude (solid lines) and shortest latency (dashed line) surface potentials were recorded to electrical stimulation of the third digit (adapted from Zimmerman, 1968). Regions (hatched areas) from which large-amplitude potentials were recorded to indentation of the second digit (adapted from Dykes, 1978) Maps from both studies are superimposed on a cytoarchitectonic map of sensorimotor cortex of the left hemisphere above the sylvian sulcus (SS) (adapted from Sanides, 1968). B, transcortical recordings under chloralose anaesthesia from area 3b (x) and 1 (y) from locations (solid circles) shown in A. SEPs recorded from the cortical surface (solid traces) and from white matter 3 mm below the cortical surface (dashed traces) Isolatency lines at the peak of the area 3b primary positivity (11 ms) and negativity (25 ms).

area 3b potentials were 3–5 ms earlier than the corresponding peaks of the area 1 potentials. Thus, despite their very different distributions on surface cortex, squirrel monkey SEPs are equivalent to those recorded in Old World monkeys and humans.

Neurophysiological plausibility of the dual radial and tangential models

Recordings from many mammalian species have shown that the initial excitation of neurons in sensory cortex evokes a positive potential as recorded from the cortical surface (the 'primary positivity') followed about 10 ms later by the 'primary negativity' (Woolsey and Fairman, 1946; Perl and Whitlock, 1955; Allison *et al.*, 1966, 1980; Towe, 1966; Zimmerman, 1968; Dykes, 1978; Arezzo *et al.*, 1979, 1981; Wood and Allison, 1981); the recordings of Figs 10–12 are representative. In the older literature this positive-negative sequence was often called the 'primary evoked response' (e.g. Towe, 1966). The primary positivity is thought to record the passive source current for active depolarizing sinks on the cell bodies and proximal apical dendrites of pyramidal cells in layers III–IV, while the primary negativity is thought to reflect the later depolarization of the superficial portion of apical dendrites (Landau, 1967; Schlag, 1973;

Werner and Whitsel, 1973; Creutzfeldt and Houchin, 1974; Wood and Allison, 1981; for a different view *see* Dykes, 1978). The tangential model makes the plausible assumption that area 3b of humans generates similar potentials.

In contrast, proponents of the dual radial model have not provided a plausible explanation for the fact that in humans and Old World monkeys the initial cortical potential recorded from parietal scalp or cortex (Figs 1–5) is negative. Desmedt and Cheron (1980) proposed that human somatosensory cortex has a functional organization different to that of other mammals, but the available anatomical evidence suggests that human somatosensory cortex is typically mammalian in gross structure (*see* Vogt, 1928; Powell and Mountcastle, 1959*a*), and there is no evidence that cortical connectivity is different in humans. An initial negativity generated in the crown of postcentral gyrus, as proposed by a version of the dual radial model (Desmedt and Bourguet, 1985), could occur due to initial depolarization of pyramidal cell apical dendrites. There is no evidence that this occurs in mature mammalian cortex, although an initial surface negativity thought to result from dendritic depolarization occurs in newborn cortex (Landau, 1967; Werner and Whitsel, 1973; Purpura, 1978). The dual radial model also fails to explain why the precentral and postcentral 20 ms and 30 ms potentials are similar in waveform but opposite in polarity. We conclude that the tangential model provides a more parsimonious and neurophysiologically plausible model of electrogenesis of the 20 ms and 30 ms potentials than does the dual radial model.

Desmedt *et al.* recently modified their earlier conclusion that P20 is generated in motor cortex, and now agree with Broughton and Allison that it is generated in area 3b (Desmedt *et al.*, 1987). Their model does not attempt to explain the origins of the 30 ms potentials. Lueders *et al.* (1983) and Tsuji and Murai (1986) proposed models similar in some respects to both the dual radial and tangential models. However, their models suppose that each region of cortex generates only a surface-positive potential, without a following negativity. This is implausible given the animal evidence reviewed above that the primary positivity is followed by a primary negativity.

The tangential+somatosensory radial model

The results discussed in the previous sections are best explained by the model of Fig. 3c, which proposes a tangential generator in area 3b of the 20 ms and 30 ms potentials, and a radial generator in area 1 of P25 and N35. This model was proposed by Allison *et al.* (1980), and incorporated the conclusions of Broughton (1969) and Giblin (1964). Broughton described the polarity inversion of the 20 ms and 30 ms potentials across the CS, and attributed them to a generator in area 3b. Giblin recorded from the surface of somatosensory cortex in a patient, and described an initial positivity (P25 as defined here) which was largest in a region medial to the location from which N20 was recorded; he concluded that it was the primary positivity of somatosensory cortex. We agree, with the proviso that P25 reflects only the primary positivity of surface cortex of the postcentral gyrus. Thus, the tangential+somatosensory radial model proposes that cortex in the anterior wall of the postcentral gyrus (consisting mainly of area 3b, but perhaps with some contribution from the portion of area 3a in the inferior wall and the portion of area 1 in the superior wall) generates the primary evoked response P20-N30, while cortex of the crown of the postcentral gyrus (consisting mainly of area 1, but perhaps with some contribution from area 2) generates, a few milliseconds later, the primary evoked response P25-N35. The complexity of the potential fields recorded from the surface of sensorimotor cortex or from the scalp reflects the different orientation of the generators in areas 3b and 1, and their asynchronous activation.

Anatomical and physiological data explain why a median nerve volley activates area 3b neurons a few milliseconds before those in area 1. At normally tolerable intensities, electrical stimulation of a mixed nerve (such as the median nerve) depolarizes motor axons and large diameter, fast conducting sensory fibres of Groups I and II. The latter derive from cutaneous receptors, muscle spindles (primary and secondary endings), Golgi tendon organs and receptors in the joint capsules. The latencies of proximal peripheral nerve, cervical cord and cortical potentials following median nerve stimulation at the wrist are all consistent with a sensory volley in fibres of Groups I and/or II, and this can be directly confirmed from the reduction in latency (with very little change in waveform) when the stimulus is delivered to the elbow rather than the wrist. There is considerable evidence that cortical SEPs are generated via the dorsal column-medial lemniscal system rather than the spinothalamic tracts (e.g. Halliday and Wakefield, 1963; Namerow, 1969; Fukushima and Mayanagi, 1975; Yu and Jones, 1985). Fibres of the medial lemniscus with higher conduction velocities project preferentially to thalamocortical relay neurons which also have higher conduction velocities (Tsumoto and Iwama, 1972). In turn, thalamic afferent fibres projecting to area 3b are larger (presumably with correspondingly higher conduction velocities) than those projecting to area 1 (Jones and Powell, 1970). Thus from at least the dorsal column nuclei rostrally, afferent input from the median nerve via the dorsal column-medial lemniscal system reaches area 3b before it reaches area 1. Furthermore, area 3b projects to area 1 (for review *see* Jones, 1986), and ablation of area 3b abolishes cutaneous responsivity in area 1, suggesting that information is processed in sequence from area 3b to area 1 (Garraghty *et al.*, 1990).

SEPs GENERATED IN OTHER CORTICAL REGIONS

Thus far we have discussed areas 3b, 1 and 4. Other regions of cerebral cortex receive somatosensory input, either directly from the thalamus or indirectly via somatosensory cortex, and might generate short-latency SEPs.

Area 2

In unit recordings from awake or anaesthetized monkeys (Arezzo *et al.*, 1979, 1981; Gardner *et al.*, 1984; Pons *et al.*, 1985; Kulics and Cauller, 1986) area 2 is responsive to stimulation of cutaneous and deep receptors, and in humans would be expected to generate SEPs with a radial orientation similar to that recorded from area 1. However, in human cortical surface recordings P25 and N35 were largest in the anterior portion of postcentral gyrus corresponding to area 1 (Figs 1–4), and neither our (Allison *et al.*, 1989*a*) nor Goldring's (Stohr and Goldring, 1969; Goldring *et al.*, 1970) transcortical recordings revealed locally generated potentials in the posterior half of somatosensory cortex corresponding to area 2. While we cannot rule out a contribution of area 2 to short-latency SEPs, there is no direct evidence that it does so. It is possible that this failure is due to inappropriate recording locations, or to the sensitivity of area 2 to anaesthetic (Powell and Mountcastle, 1959*b*) or other intraoperative conditions.

Area 3a

In the 19th century it was believed that muscles were also sense organs which participated in the conscious control of movement (Jones, 1972). This idea later became unfashionable when evidence failed to emerge that input from muscle receptors was received in the cerebral cortex. Recent thinking has now come full circle since it was demonstrated (McIntyre, 1962; Oscarsson and Rosén, 1966; Phillips *et al.*, 1971) that muscle afferent responses can be recorded in various cortical regions, principally area 3a which receives the projection of Group I muscle afferents (Jones, 1983). On the basis of its subcortical and transcortical connections, area 3a should probably be regarded as closer to sensory than to motor cortex (for review *see* Jones and Porter, 1980).

Unit discharges in area 3a of baboons occur with short latency (3.8–5.2 ms following threshold electrical stimulation of a muscle nerve at the dorsal root entry zone; Phillips *et al.*, 1971) and are also recorded in response to small muscle displacements. In rhesus monkeys Arezzo *et al.* (1981) recorded bursts of multiple unit activity in area 3a, evoked by median nerve stimulation, which were similar to those recorded in area 3b. However, whether this activity contributes to SEPs recorded from the cortical surface or scalp is unknown. In laminar recordings from the sensorimotor region of cynomolgus monkeys, no potentials evoked by median nerve stimulation that appeared to be locally generated were recorded from area 3a (McCarthy *et al.*, 1991). Perhaps this is not surprising, since the median nerve at the wrist of humans (and presumably of Old World monkeys as well) is composed mainly of cutaneous fascicles (Sunderland and Bedbrook, 1949; Schady *et al.*, 1983).

In Old World monkeys and humans area 3a is located in the fundus of the CS (Fig. 3; Vogt, 1928; Powell and Mountcastle, 1959*a*). Due to its inaccessible location no recordings in area 3a have been obtained in humans. However, it has recently been observed in cortical surface recordings that, while the later portion of N20 is attenuated when the electrical stimulus to the median nerve is delivered concurrently with a tactile 'interfering' stimulus (continuous light brushing of the palmar hand), the early portion may be unaffected (Jones *et al.*, 1991). If the affected portion represents a response to cutaneous input, the unaffected portion could represent a different modality which is impervious to interfering cutaneous stimulation. Since the unaffected portion of N20 is often recorded with opposite polarity anterior and posterior to the CS it is possible that it originates in a portion of area 3a located in the lower posterior wall of the CS. Alternatively, it is possible that interfering stimuli mainly engage rapidly-adapting cutaneous afferents, so that the relatively unaffected portion reflects activity evoked in area 3b by slowly adapting cutaneous afferents.

With regard to the possibility that area 3a might contribute to scalp-recorded SEPs, it has not been established to what extent cortical SEPs to median nerve stimulation are due to Group II cutaneous and/or joint afferents (which travel in cutaneous nerves) or to muscle afferents of Groups I and II which account for about 50% of myelinated axons present in muscle nerves (Boyd and Davey, 1968). SEPs can be recorded to stimulation of purely cutaneous nerves (such as the superficial radial) which are similar to those recorded to median nerve stimulation, but Gandevia *et al.* (1984) concluded that muscle afferents make a major contribution to the median nerve SEP, which in turn implies that area 3a likely makes a major contribution. By introducing a needle electrode into the nerve trunk and passing a small current, they were able to establish whether the electrode tip lay within a cutaneous or a muscle fascicle. Cortical SEPs could be recorded in either case, but it was the muscle fascicle response which corresponded more closely to the whole median nerve SEP in terms of its latency and maximal location on the scalp. However, other evidence conflicts with this conclusion (Halonen *et al.*, 1988). To avoid the possibility that the stimulating current might spread to adjacent fascicles, a needle electrode was used to stimulate the thenar branch of the median nerve in the palm of the hand. This is a purely muscle nerve which contains the majority of muscle fascicles present in the median nerve at the wrist. A small nerve action potential was recorded at the elbow following thenar branch stimulation, commensurate in amplitude with the size of the nerve, but cortical SEPs were very ill-defined. Equally poor cortical responses were obtained to stimulation of the much larger deep radial (muscle) nerve, in marked contrast to the excellent SEPs following superficial radial (cutaneous) nerve stimulation (Fig. 13).

A recent study by Gandevia and Burke (1990) may resolve this issue. They found that a small N20 and P25 could be recorded following microstimulation of thenar muscle afferents. They also replotted some of the waveforms of Halonen *et al.* (1988) at higher gain and concluded that N20, P25, P20 and N30 were present. However, Gandevia and Burke found that N20-P25 amplitude was on average 0.49 μV to stimulation of thenar muscle afferents, compared with 3.58 μV to stimulation of the median nerve at the wrist. Their results suggest that cortical potentials generated by muscle afferents contribute less than 15% of the voltage to median nerve SEPs.

The supplementary motor area

The supplementary motor area (SMA), first described in humans by Penfield and Welch (1951) and in monkeys by Woolsey *et al.* (1952), was conceived by them to be a smaller, less somatotopically organized version of primary motor cortex, and to be involved in postural control and vocalization. Recently, attention has shifted to the possible role of the SMA in the initiation of voluntary movement, and in the programming of sequences of learned movements (for reviews *see* Eccles, 1982; Goldberg, 1985; Wiesendanger, 1986). The SMA apparently does not receive direct somatosensory input from the thalamus, but in monkeys it does receive projections from SI, SII and area 5. Some neurons in the SMA respond to mechanical stimuli such as light pressure or limb displacement (Wiesendanger, 1986).

We have recorded SEPs from the surface of frontal mesial cortex in patients with seizures suspected of originating in this region (Allison *et al.*, 1990). In some recordings there is no evidence of potentials generated in the SMA, but in other patients large, focal potentials are recorded which do appear to be locally generated, as illustrated in Fig. 14. At posterior locations of the right mesial array (Fig. 14A, locations 7 and 8) P20-N30 potentials were recorded which were also recorded with decreasing amplitude more anteriorly, and were probably volume conducted from the hand area of somatosensory cortex. By contrast, location 6 exhibited a large, focal positivity at about 40 ms, followed by a large negativity at about 70 ms. These potentials were presumably generated in the hand representation of the SMA, since they were largest anterior to the foot area of somatosensory cortex (as localized by the large posterior tibial nerve SEP recorded from location 7, Fig. 14C). This and similar recordings do not support the suggestion of Desmedt and Bourguet (1985) that P22 is generated partly in the SMA, since the

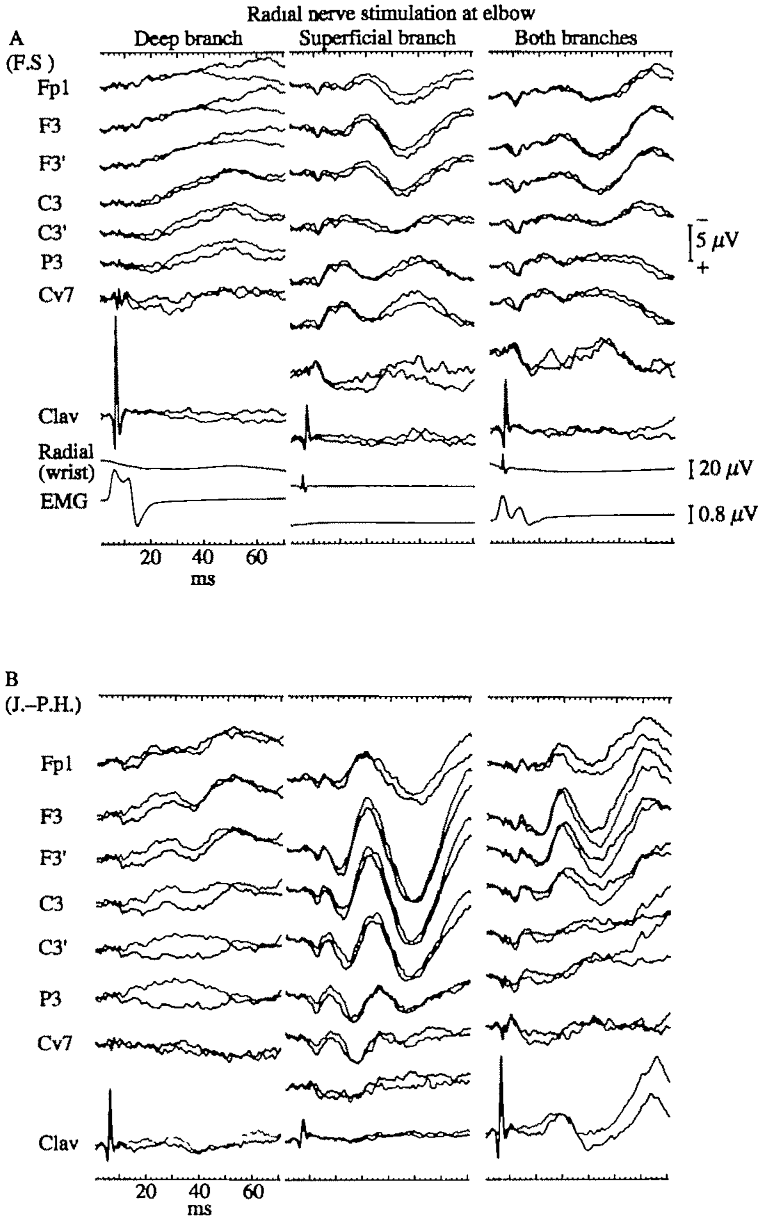

FIG. 13 Scalp, cervical and clavicular SEPs of 2 awake subjects following radial nerve stimulation at the right elbow. Superficial (cutaneous) and deep (muscle) branches were stimulated both separately and simultaneously. A, surface EMG was recorded from forearm extensor muscles following deep radial nerve stimulation but no sensory action potential was recorded from the superficial radial nerve at the wrist. A nerve volley of large amplitude was recorded from the clavicle, plus small cervical and scalp 'far-field' potentials, but no well-defined cortical response was recorded. This contrasts with the consistent cortical responses following superficial radial nerve stimulation, in addition to a distal SAP but no EMG. B, similar results in a second subject. Note that the clavicular potential following combined deep and cutaneous branch stimulation is approximately the sum of the 2 individual responses, but that the cortical responses are much less than the sum, suggesting a degree of suppressive interaction. From Halonen *et al.* (1988)

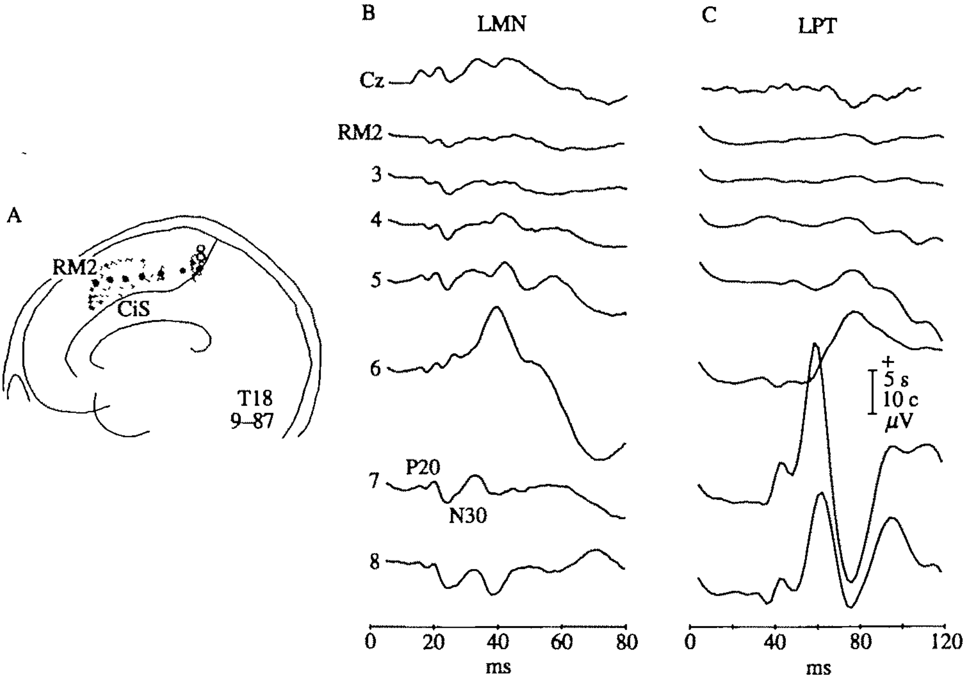

FIG. 14. SEPs recorded from mesial cortex. A, recording locations (1 cm interelectrode spacing) on right mesial (RM) cortex as determined by lateral x-ray, superimposed on the location of the SMA (stippled area) and cingulate sulcus (CiS) according to the atlas of Talairach and Szikla (1967). B, potentials evoked by stimulation of the left median nerve (LMN). C, potentials evoked by stimulation of the left posterior tibial nerve (LPT). Patient was awake and unsedated (these and other intracranial electrodes were implanted a week earlier); later the anterior corpus callosum was sectioned

earliest locally generated activity has an onset latency of 30 ms or later. The somewhat later activation of the SMA compared with somatosensory cortex is consistent with anatomical evidence suggesting that somatosensory input to the SMA is relayed via somatosensory cortex (Wiesendanger, 1986).

It has been suggested that N30 is generated in the SMA (Desmedt and Bourguet, 1985; Rossini *et al.*, 1989, 1990). However, the following considerations suggest that the SMA is unlikely to be a major contributor to this potential. Activation of mesial cortex would produce an initial positivity (for reasons discussed above) on the surface of the mesial wall and on ipsilateral frontal scalp, and a corresponding negativity on cortex or scalp of the contralateral frontal hemisphere. This potential distribution should be similar in shape and extent to the P20-N20 distribution, but with a coronal rather than an oblique orientation. Three kinds of evidence are inconsistent with these predictions. First, in the recording of Fig. 14B a short-latency positive potential was recorded from the mesial wall, as predicted, but it is too late (40 ms) to be considered a strong candidate for producing a P30-N30 potential field. However, additional intracranial recordings are needed to characterize better SEPs possibly generated in the SMA. Secondly, if N30 is generated in the SMA it should be recorded at high amplitude from the medial frontal cortical surface. For example, in the recording of Fig. 18 it should be well recorded from electrodes 16, 24 and 32, which are nearest the SMA. Instead, N30 is small at these locations and becomes progressively larger at locations approaching the hand area of sensorimotor cortex. Thirdly, the scalp topography of N30 is inconsistent with an origin in the mesial wall. The foot area of sensory cortex is also located in the mesial wall, and as would be expected it generates an initial positivity (the first peak in the waveform of Fig. 14c, location 7) which is largest at the midline and ipsilateral scalp, and a corresponding negativity which is largest over contralateral scalp (Wood, 1982; Seyal *et al.*, 1983; Lesser *et al.*, 1987). By contrast, the topography of N30-P30 as recorded either from the cortical surface (Fig. 2, *bottom*, 30 ms) or scalp (Fig. 2, *top*, 32 ms; *see also* the maps of Desmedt and Bourguet, 1985, fig. 5; Rossini *et al.*, 1989, fig. 6; Rossini *et al.*, 1990, fig. 6) clearly shows that the P30 maximum is over the contralateral parietal region, rather than over the ipsilateral frontal region as would be evoked by a generator in mesial frontal cortex.

In summary, while it would be useful for research and clinical purposes to be able to record short-latency SEPs generated in the SMA from the scalp, the currently available evidence indicates that this interesting region is not a major contributor to either P22 or N30. P22 and N30 are modified by lesions thought to involve motor cortex and other frontal lobe structures including the SMA (e.g. Mauguière *et al.*, 1983*a*; Rossini *et al.*, 1989). Thus, either these abnormalities affect somatosensory cortex directly or indirectly, as the data described here suggest, or frontal lobe structures contribute to these potentials in a manner not yet detected by intracranial recordings.

The supplementary sensory area

In 2 patients Penfield and Jasper (1954) found that electrical stimulation of parietal mesial cortex posterior to the foot sensory area evoked sensations (usually contralateral but occasionally bilateral) in the arm, face and leg. By analogy with the SMA, they postulated a supplementary sensory area (SSA) and presumed that it contained a separate representation of the body. Anatomical and single-unit evidence for an SSA in monkeys has been reviewed by Murray and Coulter (1981). In squirrel monkeys Blomquist and Lorenzini (1965) recorded SEPs from the SSA following stimulation of dorsal roots innervating the arm and trunk. So far as we are aware no SEP studies of this region have been carried out in Old World monkeys or humans. We have not examined this region systematically, but a few recordings from locations on or near the presumptive SSA have not shown evidence of locally generated activity. In cynomolgus monkeys Murray and Coulter (1981) found that most neurons in the SSA responded to mechanical stimulation of the limbs, trunk and face; no neurons with receptive fields restricted to the distal extremities were observed. This suggests that the median and posterior tibial nerve stimulation we employed may not be an adequate stimulus for SEP recordings. Further recordings in Old World monkeys and humans are needed to determine the location and responsive properties of this region.

The second somatosensory area

In monkeys the second somatosensory area (SII) is located within the upper wall of the lateral sulcus (e.g. Robinson and Burton, 1980). Data concerning the exact location and functional organization of SII in humans are scanty. Penfield and Jasper (1954) concluded from the results of cortical stimulation that SII is located partly in the upper wall of the sylvian sulcus (SS) and partly in surface cortex above the SS and below the face area of sensorimotor cortex. From the latter region Woolsey *et al.* (1979) obtained foot movement to cortical stimulation and SEPs to stimulation of the contralateral thumb in 1 patient. Thus in humans there is some evidence that SII is partially located on the lateral surface of cortex above the SS as well as in its upper wall, corresponding to portions of Brodmann's areas 40 and 43. Since much of SII is devoted to representation of the hand (Robinson and Burton, 1980), focal median nerve SEPs recorded from the perisylvian region would provide evidence of activity generated in SII.

Allison *et al.* (1989*a*) recorded from the surface of perisylvian cortex in 11 patients, but found no clear evidence of locally generated short-latency SEPs (*see also* Figs 17, 18), although longer-latency potentials attributed to SII were recorded (Allison *et al.*, 1989*b*). In 1 of 50 patients in whom cortical surface recordings were made from chronically implanted electrodes, Lüders *et al.* (1985) recorded small potentials from a site which they concluded was in SII. However, this site was anterior to the face area of motor cortex and was thus not in SII as normally defined. Short-latency activity was not detected in neuromagnetic recordings from the perisylvian region (Hari *et al.*, 1984). These results indicate that short-latency potentials generated in SII have not as yet been recorded in humans, although large short-latency SEPs have been recorded from SII in cats (e.g. Andersson, 1962). Successful recordings from SII may require direct placement of electrodes on the upper wall of the SS following temporal lobectomy; an initial attempt to make such a recording was unsuccessful.

COMPARISON OF CORTICAL SURFACE AND SCALP RECORDINGS

As the previous sections of this review have made clear, the neural origins of some SEPs are reasonably well established and agreed upon by most workers, but the generators of other potentials, particularly those recorded from frontal scalp, are still disputed. In part this results from the usual differences in perspective, recording conditions, patient samples, and so on. In addition, a major source of difference is whether SEPs are recorded from the scalp, or intracranially from the cortical surface and within the brain. It is possible that conclusions based on intracranial recordings are correct, and that different conclusions based on scalp recordings are also correct, the difference being that somewhat different sets of potentials are recorded in the 2 conditions. Therefore in this section we compare SEPs recorded from the scalp and from the cortical surface. Such a comparison has not been made previously, partly because the relevant data were not available, and partly because the (necessarily) different conditions under which scalp and intracranial recordings are obtained makes such an analysis difficult.

Contralateral potentials

Fig. 15 compares the 20 ms and 30 ms potentials recorded preoperatively from the scalp and intraoperatively from the cortical surface of 2 patients. Fig. 15A compares frontal and parietal scalp recordings with, respectively, the average of all precentral and postcentral cortical surface recordings. The amplitudes of the cortical surface potentials are of course much larger than those of the scalp recordings, but the waveforms in the 20–40 ms latency range are similar. Fig. 15B compares frontal and parietal scalp recordings with depth probe and cortical surface recordings. The 20 ms and 30 ms

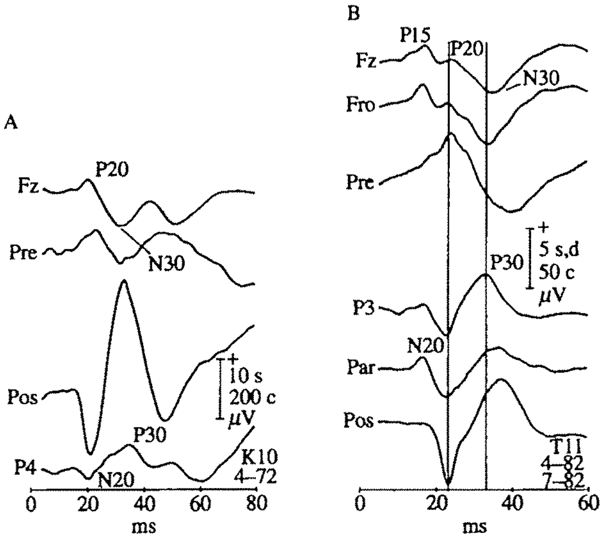

FIG. 15 Comparison of short-latency SEPs recorded from the scalp and cortical surface of 2 patients. A, recordings from frontal (Fz) and parietal (P4) scalp, and 3 wks later from the cortical surface under local anaesthesia. The trace labelled *Pre* is the average of recordings from 6 locations on motor cortex, and *Pos* is the average of recordings from 6 locations on somatosensory cortex. Patient was operated under local anaesthesia, fentanyl and droperidol for excision of a tumour in parietal cortex lateral to the hand area. B, recordings from frontal (*top three traces*) and parietal (*bottom three traces*) scalp and intracranial locations. Frontal recordings are from the scalp (Fz), the average of recordings from 10 depth probe locations in the frontal lobe (Fro), and the average of recordings from 9 locations on motor cortex (Pre). Parietal recordings are from the scalp (P3), the average of recordings from 7 depth probe locations in the parietal lobe (Par), and the average of recordings from 9 locations on somatosensory cortex (Pos). Intraoperative recordings prior to excision of the left anterior temporal lobe were obtained under local anaesthesia and fentanyl, 3 days after the scalp and depth probe recordings during quiet waking. In this and following figs *c*, *d* and *s* in the voltage calibrations refer respectively to cortical surface, depth probe and scalp recordings

potentials have similar waveforms in all 3 types of recordings. Two differences are apparent, however. In the scalp and depth recordings the subcortical P15 potential is evident, whereas it is not seen at the much lower gains used for the cortical surface recordings. Secondly, peak latencies in the cortical surface recordings are often a few milliseconds later than in the scalp and depth recordings, presumably due to intraoperative effects of sedation, anaesthesia and brain cooling (Broughton, 1969; Broughton *et al.*, 1981). Such latency changes are minimal in Fig. 15A and for the 20 ms potentials in Fig. 15B, but are apparent in the 30 ms potentials in Fig. 15B.

Fig. 16 compares frontal, central and parietal scalp and cortical surface recordings in 2 patients. The precentral P20-N30 and postcentral N20-P30 potentials recorded from frontal and parietal scalp are similar to those recorded respectively from the surface of motor and somatosensory cortex, with the usual difference that in cortical surface recordings the peak latencies are slightly later and P15 is not apparent. P25 and N35 as recorded from the central scalp (Fig. 16A, C3; 16B, C4) are similar to the largest-amplitude P25-N35 recorded from a single location on somatosensory cortex (Fig. 16A,B, CS) and to the average of potentials recorded from the region of somatosensory cortex from which large P25-N35 potentials are recorded (Fig. 16B, Central, GA).

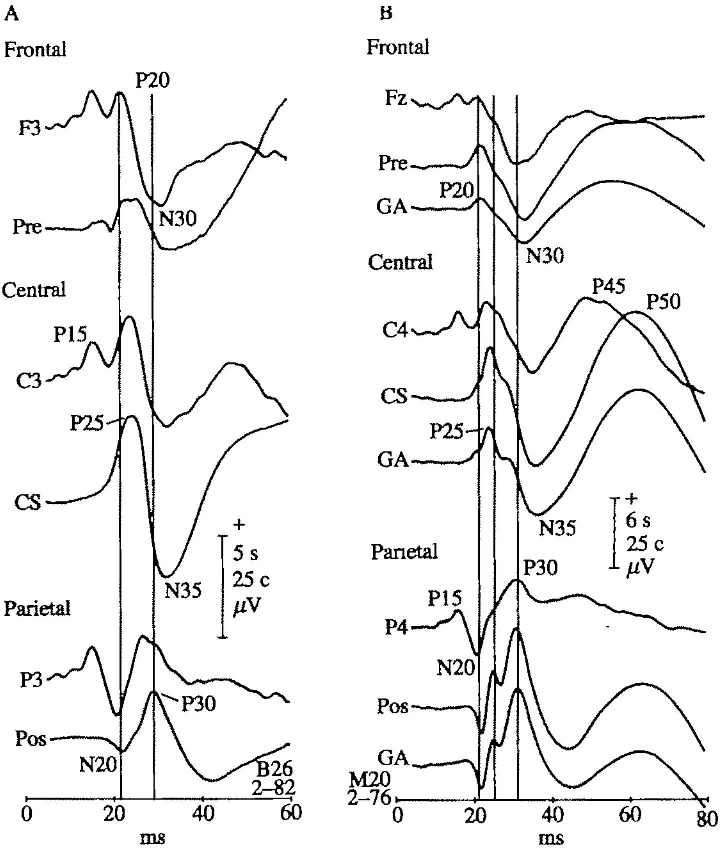

FIG. 16 Comparison of short-latency SEPs recorded from the scalp and from the cortical surface. A, the upper recordings (Frontal) are from the frontal scalp (F3) and from the precentral (Pre) location from which the largest P20-N30 was recorded from motor cortex. The middle recordings (Central) are from central scalp (C3) and from the postcentral location near the CS from which the largest P25-N35 was recorded (CS). The lower recordings (Parietal) are from parietal scalp (P3) and from the postcentral (Pos) location on somatosensory cortex from which the largest N20-P30 was recorded. Scalp recordings during quiet waking were made 3 days before the intraoperative recordings obtained under general anaesthesia (50% nitrous oxide in oxygen, with fentanyl and droperidol) for excision of a left parietal tumour not involving sensorimotor cortex. Isolatency lines are at the approximate peaks of the 20 ms (21 5 ms) and 30 ms (29.5 ms) potentials B, the upper recordings (Frontal) are from frontal scalp (Fz) from the location of the largest precentral (Pre) P20-N30 recorded from motor cortex, and the average (GA) of all 6 precentral recordings. The middle recordings (Central) are from central scalp (C4), from the location on somatosensory cortex near the CS from which the largest P25-N35 was recorded (CS), and the average (GA) of 4 such recordings. The lower recordings (Parietal) are from parietal scalp (P4), from the location from which the largest postcentral (Pos) N20-P30 was recorded from somatosensory cortex, and the average (GA) of 7 postcentral recordings from somatosensory cortex (excluding those used in the central average). Scalp recordings during quiet waking were made the day before the intraoperative recordings obtained under local anaesthesia with diazepam for biopsy of a frontal lobe lesion not involving sensorimotor cortex Isolatency lines are at the approximate peaks of the 20 ms potentials (21 ms), P25 (25 ms) and the 30 ms potentials (31 ms)

The recordings shown in Figs 15, 16 demonstrate that SEPs recorded from the cortical surface are also recorded with reasonable fidelity at the scalp, although given the spatial averaging inherent in scalp recordings most scalp locations will record some admixture of the tangential and radial potentials. This is well seen in Fig. 1B. Note the gradual transition between P20 recorded frontally, P25 recorded centrally and P30 recorded parietally, suggesting differing mixtures of these potentials at different scalp locations. The degree of this admixture is difficult to estimate quantitatively since it depends on the scalp location and on the relative strengths of the tangential and radial generators. Nevertheless, reasonable conclusions are that scalp electrodes at or anterior to the 10–20 system frontal electrodes will record primarily P20 and N30, that central scalp electrodes near C3 or C4 will record primarily P25 and N35 (with a variable amount of tangential activity depending on its exact location relative to the CS), and that scalp locations at or posterior to the 10–20 system parietal electrodes will record primarily N20 and P30.

The preceding conclusion could be incorrect if short-latency potentials recordable at the scalp were generated in other cortical regions outside somatosensory cortex, or in subcortical structures. Considering the first possibility, most investigators have concluded from intraoperative recordings that large-amplitude focal potentials are recorded only in the vicinity of the hand area of sensorimotor cortex, with amplitudes decreasing rapidly in all directions away from it (Jasper *et al.*, 1960; Kelly *et al.*, 1965; Celesia, 1979; Broughton *et al.*, 1981; Wood *et al.*, 1988; Allison *et al.*, 1989*a,b*; but *see* King and Schell, 1987). However, these recordings were spatially limited by the craniotomy and by the other limitations of intraoperative recordings already discussed. Lueders *et al.* (1983) recorded from chronically implanted electrodes in a few patients, but only in the vicinity of sensorimotor cortex. The recent use of large, chronically implanted electrode arrays on the cortical surface allows recordings from much of the surface cortex in awake, unsedated patients, as illustrated in Figs 17, 18. Fig. 17 shows SEPs recorded from a grid of electrodes spanning most

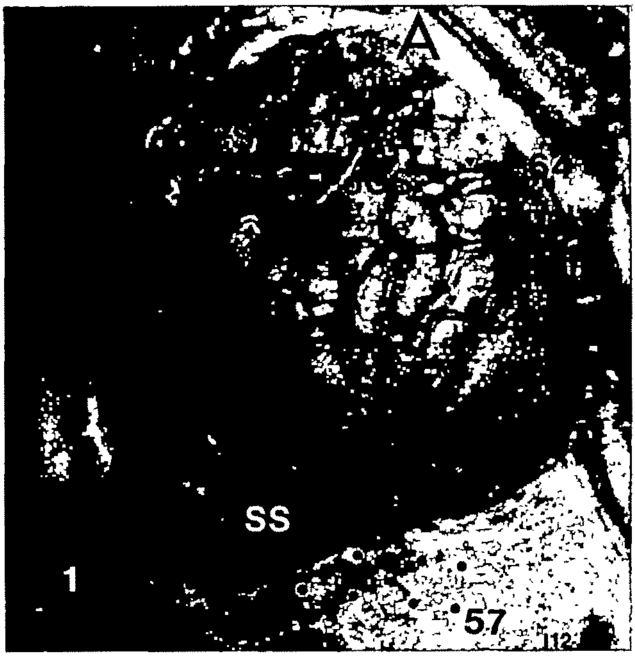

FIG 17A.

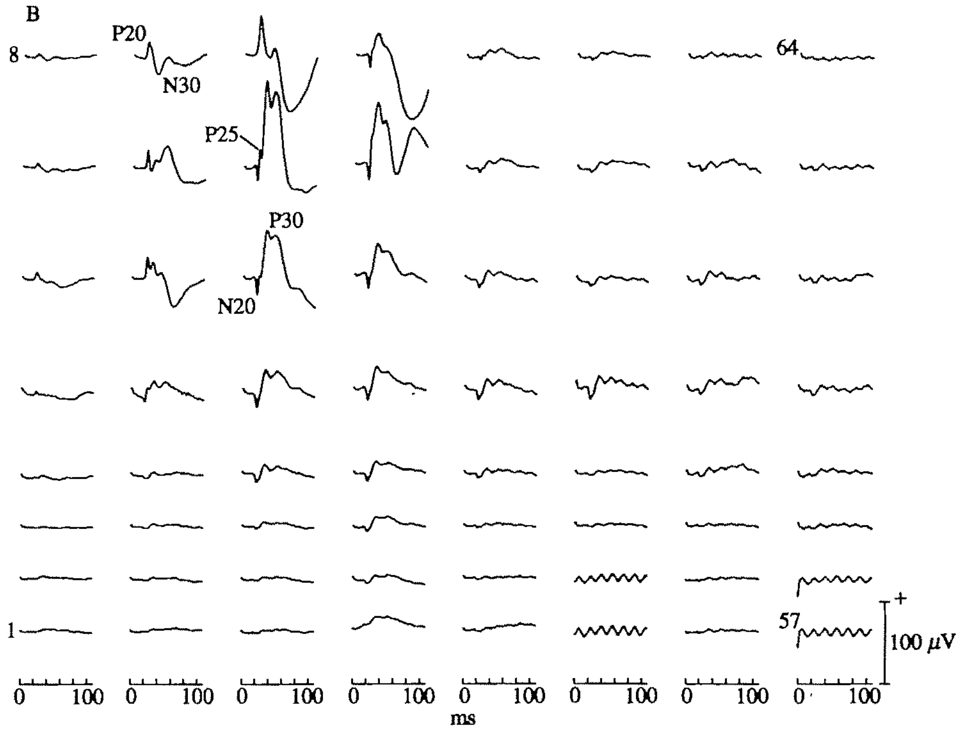

FIG. 17. SEPs recorded from the cortical surface. A, electrode locations of a 64 electrode grid (1 cm spacing) placed on the surface of parietal and temporal lobes of the left hemisphere. The digitized image was obtained from a remotely operated video camera positioned over the surgical field. A similar image with the grid in place was used to digitally mark electrode locations (triangles), which were then superimposed on the unobscured image. Estimated locations of electrodes not visible in the image are indicated by a solid circle. B, SEPs recorded during quiet waking, 1 day following grid implantation for evaluation of a parietal epileptogenic region and AVM not involving sensorimotor cortex. Electrodes 41, 42, 57 and 58 did not make adaequate contact with the brain

of the parietal cortex and the superior portion of the posterior temporal lobe. Large-amplitude focal potentials were recorded from the hand area of sensorimotor cortex, but posterior to it these potentials became increasingly smaller, and no other activity was discernible. Fig. 18 shows a similar recording from chronically implanted electrodes located at and anterior to sensorimotor cortex. Again, large-amplitude SEPs were recorded from the hand area of sensorimotor cortex, but there was no evidence of locally generated potentials in cortex of the frontal lobe. These and many other similar recordings strongly suggest that short-latency SEPs are not generated in surface cortex other than somatosensory cortex.

Subcortical potentials might also superimpose voltage on cortical potentials recorded from the scalp. The best studied subcortical activity in the 20–40 ms range is a diffuse negativity labelled N17 (Abbruzzese *et al.*, 1978; Allison, 1982; Kimura and Yamada, 1982) or N18 (Desmedt and Cheron, 1981; Mauguière *et al.*, 1983*b*; Emerson and Pedley, 1984; Urasaki *et al.*, 1990). It is subcortical in origin since it survives cortical or thalamic lesions which abolish N20 and later cortical potentials (Kimura and Yamada, 1982; Mauguière *et al.*, 1983*b*; Emerson and Pedley, 1984; Allison *et al.*, 1991);

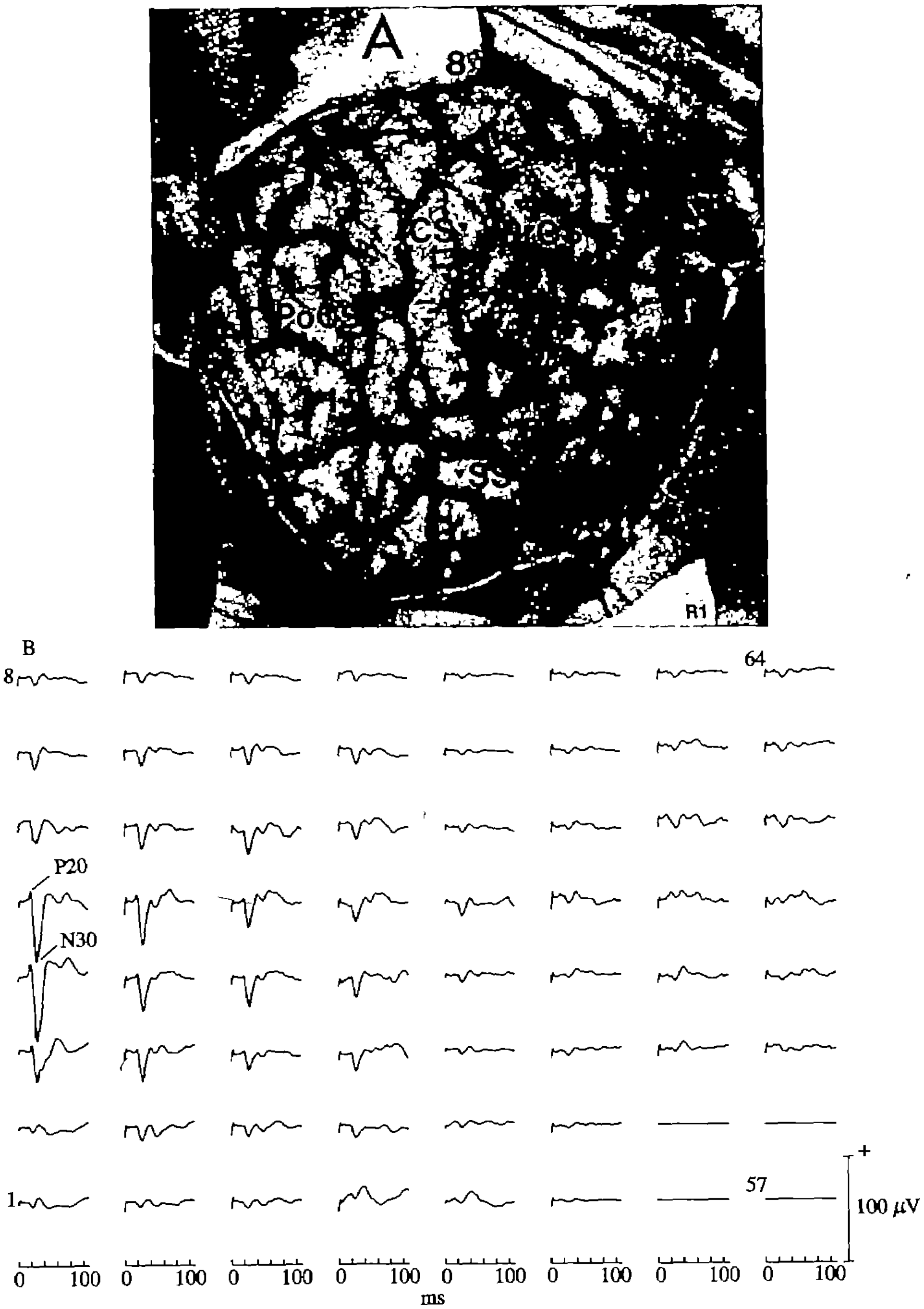

FIG. 18. SEPs recorded from the cortical surface A electrode locations (triangles) of a 64 electrode grid (1 cm spacing) placed on the frontal and temporal lobes of the right hemisphere. Electrodes 49, 50, 57 and 58 were cut off to allow grid placement around the sphenoidal wing Electrode locations determined as in Fig. 17. B, SEPs recorded during quiet waking, 1 day following grid implantation for evaluation of a frontal epileptogenic region not involving sensorimotor cortex.

intracranial recordings suggest that it may be generated in the brainstem (Urasaki *et al.*, 1990). During a craniotomy it is not possible to compare simultaneously recorded scalp and cortical surface SEPs. However, the similarity of waveform in the preoperative and intraoperative recordings (Figs 15, 16) suggests that the contribution of N17 to the scalp-recorded 20–35 ms potentials is small. On the other hand, recordings obtained from the normal hemisphere compared with those made from the hemisphere with a cortical or subcortical lesion which abolishes the cortical potentials but not N17 (Mauguière *et al.*, 1983*b*; Allison *et al.*, 1991) suggest that N17 may superimpose appreciable voltage on the 20–35 ms cortical potentials. The conclusion that N20 is of subcortical origin (for review *see* Chiappa, 1983) may be based on failure to differentiate the subcortical N17 and the cortical N20 potentials (Mauguière *et al.*, 1983*b*). P25-N35 and the 30 ms potentials are agreed by all workers to be of cortical origin, but the later portion of N17, which seems to persist until about 40 ms (Mauguière *et al.*, 1983*b*), may affect measurement of their amplitude.

Ipsilateral potentials

Potentials in the 20–40 ms latency range can be recorded from ipsilateral scalp. For example, in the topographic maps of Fig. 2, *top*, note that the distributions of the 20 ms and 30 ms potentials extend ipsilaterally across the midline. This is particularly so for the precentral P20 and N30 distributions because the oblique orientation of the CS, combined with the curvature of somatosensory cortex in the hand area (Fig. 6), causes the major axis of the dipolar generators to point toward the frontal midline, resulting in a frontal maximum in the vicinity of Fz (e.g. Fig. 2, *top*, at 32 ms). Such ipsilateral distributions have been interpreted as indicating that ipsilateral sensorimotor cortex may respond to afferent stimulation (Desmedt and Cheron, 1980). However, cortical surface recordings show that short-latency SEPs are evoked only by contralateral stimulation; stimulation of the ipsilateral median nerve produces no detectable activity (Goldring *et al.*, 1970; Lueders *et al.*, 1983; Wood *et al.*, 1988; Allison *et al.*, 1989*a*). This is consistent with the often-reported finding that neurons in the hand area of monkey somatosensory cortex respond only to contralateral stimulation. In deeper layers of cat somatosensory cortex some neurons (*m* neurons) respond to ipsilateral stimulation, but their activation contributes negligibly to the primary evoked potentials (Towe, 1966) analogous to the human short-latency potentials. If *m* neurons are present in human somatosensory cortex their activation apparently does not generate short-latency potentials recordable at the cortical surface.

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REFERENCES

ABBRUZZESE M, FAVALE E, LEANDRI M, RATTO S (1978) New subcortical components of the cerebral somatosensory evoked potential in man. *Acta Neurologica Scandinavica*, **58**, 325–332.

Abbruzzese G, Dall'Agata D, Morena M, Reni L, Favale E (1990) Abnormalities of parietal and prerolandic somatosensory evoked potentials in Huntington's disease. *Electroencephalography and Clinical Neurophysiology,* **77,** 340–346.

Allison T (1982) Scalp and cortical recordings of initial somatosensory cortex activity to median nerve stimulation in man. *Annals of the New York Academy of Sciences,* **388,** 671–678.

Allison T, Goff WR, Sterman MB (1966) Cerebral somatosensory responses evoked during sleep in the cat. *Electroencephalography and Clinical Neurophysiology,* **21,** 461–468.

Allison T, Goff WR, Williamson PD, Van Gilder JC (1980) On the neural origin of early components of the human somatosensory evoked potential. In: *Clinical Uses of Cerebral, Brainstem and Spinal Somatosensory Evoked Potentials. Progress in Clinical Neurophysiology,* Volume 7. Edited by J. E. Desmedt. Basel: Karger, pp. 51–68.

Allison T, McCarthy G, Wood CC, Darcey TM, Spencer DD, Williamson PD (1989*a*) Human cortical potentials evoked by stimulation of the median nerve. I. Cytoarchitectonic areas generating short-latency activity. *Journal of Neurophysiology,* **62,** 694–710.

Allison T, McCarthy G, Wood CC, Williamson PD, Spencer DD (1989*b*) Human cortical potentials evoked by stimulation of the median nerve. II. Cytoarchitectonic areas generating long-latency activity. *Journal of Neurophysiology,* **62,** 711–722.

Allison T, McCarthy G, Spencer DD, Jasiorkowski J (1990) Functional localization of structures of the mesial wall of human cortex by cortical stimulation and recording of somatosensory evoked potentials. *13th Joint Meeting of EEG and Clinical Neurophysiology,* Prague, May, 1990.

Allison T, Wood CC, McCarthy G, Spencer DD (1991) Cortical somatosensory evoked potentials: II. Effects of excision of somatosensory or motor cortex in humans and monkeys. *Journal of Neurophysiology,* **66,** 64–82.

Amassian VE, Waller HJ, Macy WJ (1964) Neural mechanism of the primary somatosensory evoked potential. *Annals of the New York Academy of Sciences,* **112,** 5–32.

Andersson SA (1962) Projection of different spinal pathways to the second somatic sensory area in cat. *Acta Physiologica Scandinavica,* **56,** Supplement 194, 1–74.

Arezzo J, Legatt AD, Vaughan HG (1979) Topography and intracranial sources of somatosensory evoked potentials in the monkey. I. Early components. *Electroencephalography and Clinical Neurophysiology,* **46,** 155–172.

Arezzo JC, Vaughan HG, Legatt AD (1981) Topography and intracranial sources of somatosensory evoked potentials in the monkey. II. Cortical components. *Electroencephalography and Clinical Neurophysiology,* **51,** 1–18.

Bantli H (1974) Analysis of difference between potentials evoked by climbing fibers in cerebellum of cat and turtle. *Journal of Neurophysiology,* **37,** 573–593.

Blomquist AJ, Lorenzini CA (1965) Projection of dorsal roots and sensory nerves to cortical sensory motor regions of squirrel monkey. *Journal of Neurophysiology,* **28,** 1195–1205.

Boyd IA, Davey MR (1968) *Composition of Peripheral Nerves.* Edinburgh: E. and S. Livingstone.

Broughton R (1969) Discussion. In: *Average Evoked Potentials: Methods, Results, and Evaluations.* Edited by E. Donchin and D. B. Lindsley. Washington: National Aeronautics and Space Administration, pp. 79–84.

Broughton R, Rasmussen T, Branch C (1981) Scalp and direct cortical recordings of somatosensory evoked potentials in man (circa 1967). *Canadian Journal of Psychology,* **35,** 136–158.

Celesia GG (1979) Somatosensory evoked potentials recorded directly from human thalamus and Sm I cortical area. *Archives of Neurology, Chicago,* **36,** 399–405.

Chiappa KH (1983) *Evoked Potentials in Clinical Medicine.* New York: Raven Press.

Cohen D, Cuffin BN (1983) Demonstration of useful differences between magnetoencephalogram and electroencephalogram. *Electroencephalography and Clinical Neurophysiology,* **56,** 38–51.

Cohen LG, Starr A (1987) Localization, timing and specificity of gating of somatosensory evoked potentials during active movement in man. *Brain,* **110,** 451–467.

Creutzfeldt O, Houchin J (1974) Neuronal basis of EEG-waves. In: *Handbook of Electroencephalography and Clinical Neurophysiology,* Volume 2, Part C. Edited by A. Rémond Amsterdam: Elsevier, pp. 2C-5–2C-55.

Deiber MP, Giard MH, Mauguière F (1986) Separate generators with distinct orientations for N20 and P22 somatosensory evoked potentials to finger stimulation? *Electroencephalography and Clinical Neurophysiology,* **65,** 321–334.

DELMAS A, PERTUISET B (1959) *Cranio-Cerebral Topometry in Man.* Springfield, IL: Charles C. Thomas.

DESMEDT JE, CHERON G (1980) Somatosensory evoked potentials to finger stimulation in healthy octogenarians and in young adults: wave forms, scalp topography and transit times of parietal and frontal components. *Electroencephalography and Clinical Neurophysiology*, **50**, 404–425.

DESMEDT JE, CHERON G (1981) Non-cephalic reference recording of early somatosensory potentials to finger stimulation in adult or aging normal man: differentiation of widespread N18 and contralateral N20 from the prerolandic P22 and N30 components. *Electroencephalography and Clinical Neurophysiology*, **52**, 553–570.

DESMEDT JE, BOURGUET M (1985) Color imaging of parietal and frontal somatosensory potential fields evoked by stimulation of median or posterior tibial nerve in man. *Electroencephalography and Clinical Neurophysiology*, **62**, 1–17.

DESMEDT JE, NGUYEN TH, BOURGUET M (1987) Bit-mapped color imaging of human evoked potentials with reference to the N20, P22, P27 and N30 somatosensory responses. *Electroencephalography and Clinical Neurophysiology*, **68**, 1–19.

DE WEERD AW, LOOIJENGA A, VELDHUIZEN RJ, VAN HUFFELEN AC (1985) Somatosensory evoked potentials in minor cerebral ischaemia: diagnostic significance and changes in serial records. *Electroencephalography and Clinical Neurophysiology*, **62**, 45–55.

DYKES RW (1978) The anatomy and physiology of the somatic sensory cortical regions. *Progress in Neurobiology*, **10**, 33–88.

ECCLES JC (1982) The initiation of voluntary movements by the supplementary motor area. *Archiv fur Psychiatrie und Nervenkrankheiten*, **231**, 423–441.

EMERSON RG, PEDLEY TA (1984) Generator sources of median somatosensory evoked potentials. *Journal of Clinical Neurophysiology*, **1**, 203–218.

FREEMAN WJ (1972) Depth recording of averaged evoked potential of olfactory bulb. *Journal of Neurophysiology*, **35**, 780–796.

FREEMAN WJ (1975) *Mass Action in the Nervous System.* New York: Academic Press.

FUKUSHIMA T, MAYANAGI Y (1975) Neurophysiological examination (SEP) for the objective diagnosis of spinal lesions. In: *Advances in Neurosurgery* 2. Edited by W. Klug, M. Brock, M. Klinger and O. Spoerri. Berlin: Springer, pp. 158–168.

GANDEVIA SC, BURKE D, MCKEON B (1984) The projection of muscle afferents from the hand to cerebral cortex in man. *Brain*, **107**, 1–13.

GANDEVIA SC, BURKE D (1990) Projection of thenar muscle afferents to frontal and parietal cortex of human subjects. *Electroencephalography and Clinical Neurophysiology*, **77**, 353–361.

GARDNER EP, HÄMÄLÄINEN HA, WARREN S, DAVIS J, YOUNG W (1984) Somatosensory evoked potentials (SEPs) and cortical single unit responses elicited by mechanical tactile stimuli in awake monkeys. *Electroencephalography and Clinical Neurophysiology*, **58**, 537–552.

GARRAGHTY PE, FLORENCE SL, KAAS JH (1990) Ablations of areas 3a and 3b of monkey somatosensory cortex abolish cutaneous responsivity in area 1. *Brain Research, Amsterdam*, **528**, 165–169.

GIBLIN DR (1964) Somatosensory evoked potentials in healthy subjects and in patients with lesions of the nervous system. *Annals of the New York Academy of Sciences*, **112**, 93–142.

GOFF GD, MATSUMIYA Y, ALLISON T, GOFF WR (1977) The scalp topography of human somatosensory and auditory evoked potentials. *Electroencephalography and Clinical Neurophysiology*, **42**, 57–76.

GOFF WR, ALLISON T, VAUGHAN HG (1978) The functional neuroanatomy of event related potentials. In: *Event-Related Brain Potentials in Man.* Edited by E. Callaway, P. Tueting and S. H. Koslow. New York and London: Academic Press, pp. 1–79.

GOLDBERG G (1985) Supplementary motor area structure and function: review and hypotheses. *Behavioral and Brain Sciences*, **8**, 567–615.

GOLDRING S, ARAS E, WEBER PC (1970) Comparative study of sensory input to motor cortex in animals and man. *Electroencephalography and Clinical Neurophysiology*, **29**, 537–550.

HALLIDAY AM, WAKEFIELD GS (1963) Cerebral evoked potentials in patients with dissociated sensory loss. *Journal of Neurology, Neurosurgery, and Psychiatry*, **26**, 211–219.

HALONEN, J-P, JONES S, SHAWKAT F (1988) Contribution of cutaneous and muscle afferent fibres to cortical SEPs following median and radial nerve stimulation in man. *Electroencephalography and Clinical Neurophysiology*, **71**, 331–335.

Hari R, Reinikainen K, Kaukoranta E, Hämäläinen M, Ilmoniemi R, Penttinen A *et al.* (1984) Somatosensory evoked cerebral magnetic fields from SI and SII in man. *Electroencephalography and Clinical Neurophysiology*, **57**, 254–263.

Homan RW, Herman J, Purdy P (1987) Cerebral location of international 10-20 system electrode placement. *Electroencephalography and Clinical Neurophysiology*, **66**, 376–382.

Jasper HH (1958) Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalography and Clinical Neurophysiology*, **10**, 370–375.

Jasper H, Lende R, Rasmussen T (1960) Evoked potentials from the exposed somato-sensory cortex in man. *Journal of Nervous and Mental Disease*, **130**, 526–537.

Jones EG (1972) The development of the 'muscular sense' concept in the nineteenth century and the work of H. Charlton Bastian. *Journal of the History of Medicine and Allied Sciences*, **27**, 298–311.

Jones EG (1983) The nature of the afferent pathways conveying short-latency inputs to primate motor cortex. *Advances in Neurology*, **39**, 263–285.

Jones EG (1986) Connectivity of the primate sensory-motor cortex. In: *Cerebral Cortex*, Volume 5, *Sensory-Motor Areas and Aspects of Cortical Connectivity*. Edited by E. G. Jones and A. Peters New York and London: Plenum Press, pp. 113–183.

Jones EG, Powell TPS (1970) Connexions of the somatic sensory cortex of the rhesus monkey: III.—Thalamic connexions. *Brain*, **93**, 37–56.

Jones EG, Porter R (1980) What is area 3a? *Brain Research Reviews*, **2**, 1–43.

Jones SJ, Power CN (1984) Scalp topography of human somatosensory evoked potentials: the effect of interfering tactile stimulation applied to the hand. *Electroencephalography and Clinical Neurophysiology*, **58**, 25–36.

Jones SJ, Allison T, McCarthy G, Wood CC (1991) Tactile interference differentiates subcomponents of N20, P20 and P29 in the human cortical surface SEP. *Electroencephalography and Clinical Neurophysiology*. In press.

Juliano SL, Whitsel BL (1985) Metabolic labeling associated with index finger stimulation in monkey SI: between animal variability. *Brain Research, Amsterdam*, **342**, 242–251.

Kaas JH, Sur M, Nelson RJ, Merzenich MM (1981) The postcentral somatosensory cortex: multiple representations of the body in primates. In: *Cortical Sensory Organization*, Volume 1, *Multiple Somatic Areas*. Edited by C. N. Woolsey. Clifton, NJ: Humana Press, pp. 29–61.

Kelly DL, Goldring S, O'Leary JL (1965) Average evoked somatosensory responses from exposed cortex of man. *Archives of Neurology, Chicago*, **13**, 1–9.

Kimura J, Yamada T (1982) Short-latency somatosensory evoked potentials following median nerve stimulation. *Annals of the New York Academy of Sciences*, **388**, 689–694.

King RB, Schell GR (1987) Cortical localization and monitoring during cerebral operations. *Journal of Neurosurgery*, **67**, 210–219.

Klee M, Rall W (1977) Computed potentials of cortically arranged populations of neurons. *Journal of Neurophysiology*, **40**, 647–666.

Kulics AT, Cauller LJ (1986) Cerebral cortical somatosensory evoked responses, multiple unit activity and current source-densities: their interrelationships and significance to somatic sensation as revealed by stimulation of the awake monkey's hand. *Experimental Brain Research*, **62**, 46–60.

Landau WM (1967) Evoked potentials. In· *The Neurosciences*. Edited by G. C. Quarton, T. Melnechuk and F. O. Schmitt. New York: Rockefeller University Press, pp. 469–482.

Lesser RP, Lüders H, Dinner DS, Hahn J, Morris H, Wyllie E *et al.* (1987) The source of 'paradoxical lateralization' of cortical evoked potentials to posterior tibial nerve stimulation. *Neurology, Cleveland*, **37**, 82–88.

Llinás R, Nicholson C (1974) Analysis of field potentials in the central nervous system. In: *Handbook of Electroencephalography and Clinical Neurophysiology*, Volume 2, Part B. Edited by A. Rémond. Amsterdam: Elsevier, pp. 2B-61–2B-92.

Lüders H, Lesser RP, Dinner DS, Hahn JF, Salanga V, Morris HH (1985) The second sensory area in humans: evoked potential and electrical stimulation studies. *Annals of Neurology*, **17**, 177–184.

Lueders H, Lesser RP, Hahn J, Dinner DS, Klem G (1983) Cortical somatosensory evoked potentials in response to hand stimulation. *Journal of Neurosurgery*, **58**, 885–894.

Maccabee PJ, Pinkhasov EI, Cracco RQ (1983) Short latency somatosensory evoked potentials to median nerve stimulation: effect of low frequency filter. *Electroencephalography and Clinical Neurophysiology*, **55**, 34–44.

McCarthy G, Wood CC, Allison T (1991) Cortical somatosensory evoked potentials: I. Recordings in the monkey *Macaca fascicularis*. *Journal of Neurophysiology*, **66**, 53–63.

McIntyre AK (1962) Cortical projection of impulses in the interosseous nerve of the cat's hind limb. *Journal of Physiology, London*, **163**, 46–60.

McKenna TM, Whitsel BL, Dreyer DA (1982) Anterior parietal cortical topographic organization in macaque monkey: a reevaluation. *Journal of Neurophysiology*, **48**, 289–317.

Mauguière F, Desmedt JE, Courjon J (1983*a*) Astereognosis and dissociated loss of frontal or parietal components of somatosensory evoked potentials in hemispheric lesions: detailed correlations with clinical signs and computerized tomographic scanning. *Brain*, **106**, 271–311.

Mauguière F, Desmedt JE, Courjon J (1983*b*) Neural generators of N18 and P14 far-field somatosensory evoked potentials studied in patients with lesion of thalamus or thalamo-cortical radiations. *Electroencephalography and Clinical Neurophysiology*, **56**, 283–292.

Mitzdorf U, Singer W (1980) Monocular activation of visual cortex in normal and monocularly deprived cats: an analysis of evoked potentials. *Journal of Physiology, London*, **304**, 203–220.

Murray EA, Coulter JD (1981) Supplementary sensory area: the medial parietal cortex in the monkey. In: *Cortical Sensory Organization*, Volume 1, *Multiple Somatic Areas*. Edited by C. N. Woolsey. Clifton, NJ: Humana Press, pp. 167–195.

Namerow NS (1969) Somatosensory evoked responses following cervical cordotomy. *Bulletin of the Los Angeles Neurological Societies*, **34**, 184–188.

Nogueira MC, Brunko E, Vandesteen A, De Rood M, Zegers de Beyl D (1989) Differential effects of isoflurane on SEP recorded over parietal and frontal scalp. *Neurology, Cleveland*, **39**, 1210–1215.

Okada YC, Tanenbaum R, Williamson SJ, Kaufman L (1984) Somatotopic organization of the human somatosensory cortex revealed by neuromagnetic measurements. *Experimental Brain Research*, **56**, 197–205.

Oscarsson O, Rosén I (1966) Short-latency projections to the cat's cerebral cortex from skin and muscle afferents in the contralateral forelimb. *Journal of Physiology, London*, **182**, 164–184.

Papakostopoulos D, Crow HJ (1980) Direct recording of the somatosensory evoked potentials from the cerebral cortex of man and the difference between precentral and postcentral potentials. In: *Clinical Uses of Cerebral, Brainstem and Spinal Somatosensory Evoked Potentials. Progress in Clinical Neurophysiology*, Volume 7. Edited by J. E. Desmedt. Basel: Karger, pp. 15–26.

Papakostopoulos D, Crow HJ (1984) The precentral somatosensory evoked potential. *Annals of the New York Academy of Sciences*, **425**, 256–261.

Penfield W, Welch K (1951) The supplementary motor area of the cerebral cortex: a clinical and experimental study. *Archives of Neurology and Psychiatry, Chicago*, **66**, 289–317.

Penfield W, Jasper H (1954) *Epilepsy and the Functional Anatomy of the Human Brain*. London: J. and A. Churchill.

Perl ER, Whitlock DG (1955) Potentials evoked in cerebral somatosensory region. *Journal of Neurophysiology*, **18**, 486–501.

Phillips CG, Powell TPS, Wiesendanger M (1971) Projection from low-threshold muscle afferents of hand and forearm to area 3a of baboon's cortex. *Journal of Physiology, London*, **217**, 419–446.

Pons TP, Garraghty PE, Cusick CG, Kaas JH (1985) The somatotopic organization of area 2 in macaque monkeys. *Journal of Comparative Neurology*, **241**, 445–466.

Powell TPS, Mountcastle VB (1959*a*) The cytoarchitecture of the postcentral gyrus of the monkey *Macaca mulatta*. *Bulletin of the Johns Hopkins Hospital*, **105**, 108–131.

Powell TPS, Mountcastle VB (1959*b*) Some aspects of the functional organization of the cortex of the postcentral gyrus of the monkey: a correlation of findings obtained in a single unit analysis with cytoarchitecture. *Bulletin of the Johns Hopkins Hospital*, **105**, 133–162.

Purpura DP (1978) Commentary. In: *Event-Related Brain Potentials in Man*. Edited by E. Callaway, P. Tueting and S. H. Koslow. New York and London: Academic Press, pp. 81–87.

Robinson CJ, Burton H (1980) Somatotopographic organization in the second somatosensory area of *M. fascicularis*. *Journal of Comparative Neurology*, **192**, 43–67.

Rossini PM, Babiloni F, Bernardi G, Cecchi L, Johnson PB, Malentacca A *et al.* (1989) Abnormalities of short-latency somatosensory evoked potentials in parkinsonian patients. *Electroencephalography and Clinical Neurophysiology*, **74**, 277–289.

Rossini PM, Paradiso C, Zarola F, Mariorenzi R, Traversa R, Martino G *et al.* (1990) Bit-mapped somatosensory evoked potentials and muscular reflex responses in man: comparative analysis in different experimental protocols. *Electroencephalography and Clinical Neurophysiology,* **77,** 266–275.

SANIDES F (1968) The architecture of the cortical taste nerve areas in squirrel monkey (*Saimiri sciureus*) and their relationship to insular, sensorimotor and prefrontal regions. *Brain Research, Amsterdam,* **8,** 97–124.

SCHADY W, OCHOA JL, TOREBJÖRK HE, CHEN LS (1983) Peripheral projections of fascicles in the human median nerve. *Brain,* **106,** 745–760.

SCHLAG J (1973) Generation of brain evoked potentials. In: *Bioelectric Recording Techniques,* Part A: *Cellular Processes and Brain Potentials.* Edited by R. F. Thompson and M. M. Patterson. New York and London: Academic Press, pp. 273–316.

SEYAL M, EMERSON RG, PEDLEY TA (1983) Spinal and early scalp-recorded components of the somatosensory evoked potential following stimulation of the posterior tibial nerve. *Electroencephalography and Clinical Neurophysiology,* **55,** 320–330.

SIDMAN RD, GIAMBALVO V, ALLISON T, BERGEY P (1978) A method for localization of sources of human cerebral potentials evoked by sensory stimuli. *Sensory Processes,* **2,** 116–129.

SLIMP JC, TAMAS LB, STOLOV WC, WYLER AR (1986) Somatosensory evoked potentials after removal of somatosensory cortex in man. *Electroencephalography and Clinical Neurophysiology,* **65,** 111–117.

SPENCER SS, SPENCER DD, WILLIAMSON PD, MATTSON RH (1982) The localizing value of depth electroencephalography in 32 patients with refractory epilepsy. *Annals of Neurology,* **12,** 248–253.

STOHR PE, GOLDRING S (1969) Origin of somatosensory evoked scalp responses in man. *Journal of Neurosurgery,* **31,** 117–127.

SUNDERLAND S, BEDBROOK GM (1949) The cross-sectional area of peripheral nerve trunks occupied by the fibres representing individual muscular and cutaneous branches. *Brain,* **72,** 613–624.

TALAIRACH J, SZIKLA G (1967) *Atlas of Stereotaxic Anatomy of the Telencephalon: Anatomo-Radiological Studies.* Paris: Masson.

TOWE AL (1966) On the nature of the primary evoked response. *Experimental Neurology,* **15,** 113–139.

TSUJI S, MURAI Y (1986) Scalp topography and distribution of cortical somatosensory evoked potentials to median nerve stimulation. *Electroencephalography and Clinical Neurophysiology,* **65,** 429–439.

TSUMOTO T, IWAMA K (1972) Conduction velocities of lemniscal and thalamocortical fibers: their somatotopic differentiation and a rule of connection in the thalamic relay system. *Brain Research, Amsterdam,* **44,** 666–669.

URASAKI E, WADA S, KADOYA C, YOKOTA A, MATSUOKA S, SHIMA F (1990) Origin of scalp far-field N18 of SSEPs in response to median nerve stimulation. *Electroencephalography and Clinical Neurophysiology,* **77,** 39–51.

VOGT M (1928) Über omnilaminäre Strukturdifferenzen und lineare Grenzen der architektonischen Felder der hinteren Zentralwindung des Menschen. *Journal für Psychologie und Neurologie, Leipzig,* **35,** 177–193.

WERNER G, WHITSEL BL (1973) Functional organization of the somatosensory cortex. In: *Handbook of Sensory Physiology,* Volume 2: *Somatosensory System.* Edited by A. Iggo. Berlin: Springer, pp. 621–700,

WIESENDANGER M (1986) Recent developments in studies of the supplementary motor area of primates. *Reviews of Physiology, Biochemistry and Pharmacology,* **103,** 1–59.

WILLIAMSON SJ, KAUFMAN L (1981) Biomagnetism. *Journal of Magnetism and Magnetic Materials,* **22,** 129–201.

WOOD CC (1982) Application of dipole localization methods to source identification of human evoked potentials. *Annals of the New York Academy of Sciences,* **388,** 139–155.

WOOD CC, ALLISON T (1981) Interpretation of evoked potentials: a neurophysiological perspective. *Canadian Journal of Psychology,* **35,** 113–135.

WOOD CC, COHEN D, CUFFIN BN, YARITA M, ALLISON T (1985) Electrical sources in human somatosensory cortex: identification by combined magnetic and potential recordings. *Science,* **227,** 1051–1053.

WOOD CC, SPENCER DD, ALLISON T, MCCARTHY G, WILLIAMSON PD, GOFF WR (1988) Localization of human sensorimotor cortex during surgery by cortical surface recording of somatosensory evoked potentials. *Journal of Neurosurgery,* **68,** 99–111.

WOOLSEY CN, FAIRMAN D (1946) Contralateral, ipsilateral, and bilateral representation of cutaneous receptors in somatic areas I and II of the cerebral cortex of pig, sheep, and other mammals. *Surgery,* **19,** 684–702.

Woolsey CN, Settlage PH, Meyer DR, Sencer W, Hamuy TP, Travis AM (1952) Patterns of localization in precentral and 'supplementary' motor areas and their relation to the concept of a premotor area. *Research Publications: Association for Research in Nervous and Mental Diseases,* **30,** 238–264.

Woolsey CN, Erickson TC, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. *Journal of Neurosurgery,* **51,** 476–506.

Yamada T, Kayamori R, Kimura J, Beck DO (1984) Topography of somatosensory evoked potentials after stimulation of the median nerve. *Electroencephalography and Clinical Neurophysiology,* **59,** 29–43.

Yu YL, Jones SJ (1985) Somatosensory evoked potentials in cervical spondylosis: correlation of median, ulnar and posterior tibial nerve responses with clinical and radiological findings. *Brain,* **108,** 273–300.

Zimmerman ID (1968) A triple representation of the body surface in the sensorimotor cortex of the squirrel monkey. *Experimental Neurology,* **20,** 415–431.

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Brain (1991), **114**, 2505–2520

PARAESTHESIAS ARE ELICITED BY SINGLE PULSE, MAGNETIC COIL STIMULATION OF MOTOR CORTEX IN SUSCEPTIBLE HUMANS

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SUMMARY

A minority of normal humans experience paraesthesias (usually tingling) projected to the contralateral hand in response to individual transcranial magnetic coil (MC) pulses. The cortical source of the paraesthesias was sought by comparing their incidence with that of muscle responses to focal MC stimulation with either a figure 8 MC or with edge stimulation of a tilted round MC in 4 susceptible subjects. In all 4, paraesthesias were best felt with MC stimulation either at, or anterior to sites yielding movement, implying an initial source in precentral gyrus (and possible premotor cortex), rather than parietal cortex. In the two subjects exhibiting the strongest paraesthesias, the threshold for the paraesthesias was less than that for movement in the relaxed arm. The optimal site of the paraesthesias within the hand was usually in the digits, but differed among subjects. Motor responses and paraesthesias following a given stimulus occurred at different sites in the hand, implying that excitation of differing sets of motor cortical neurons subserved sensory and motor responses.

In only one subject were the paraesthesias sufficiently reproducible to warrant interacting electrical digital and transcranial MC pulses. The data suggested that central processing of the response to the MC pulse is slowed by an antecedent digital stimulus, but the delay for perception of each type of stimulus does not greatly differ.

The central sense of movement (Amassian *et al.*, 1989*a*) elicited by MC stimulation of motor cortex is compared with the paraesthesias. Both are attributed to brief, high frequency discharge by motor cortical neurons accessing the perceptual system more readily than after excitation of post-central gyrus, which requires prolonged repetitive stimulation (Libet *et al.*, 1964). Given also the normal pattern of muscle responses in the 4 subjects, their paraesthesias are best explained by a heightened sensitivity of the perceptual system to the motor cortical response to MC stimulation.

INTRODUCTION

Paraesthesias projected to a contralateral site on the body have long been known to follow repetitive electrical stimulation of the exposed human cerebral cortex (Foerster, 1936; Penfield and Boldrey, 1937). Significantly, galvanic stimulation of the post-central gyrus was reported to elicit only a localized movement, repetitive stimulation being required to elicit a sensation (Foerster, 1936). In a careful parametric study, Libet *et al.* (1964),

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while generally confirming the necessity for repetitive stimulation, noted that subjects at times described a 'tingle' following a single stimulus. However, they attributed such reports to a misinterpretation of the afferent feedback from a fleeting movement elicited by the stimulus.

The magnetic coil (MC) stimulator introduced by Barker *et al.* (1985, 1987) made possible stimulation of the unexposed cerebral cortex of normal humans with minimal discomfort. However, until very recently (Amassian *et al.*, 1990*a*), MC stimulators could only deliver individual pulses at minimum intervals of several seconds. Not surprisingly, when stimulating an initial group of colleagues with individual MC pulses, we failed to elicit any report of paraesthesias to transcranial stimulation over either frontal or parietal lobes. By contrast, individual MC pulses delivered to motor cortex elicited reports of localized movement; these persisted in the ischaemically paralysed limb and were attributed to a 'central' sense of movement related to a corollary discharge (Amassian *et al.*, 1989*a*). Later, while routinely stimulating other colleagues at SUNY Health Science Center at Brooklyn, we encountered one who carefully distinguished his experience of paraesthesias from sense of movement and reliably reported the difference in repeated sessions. A preliminary report of the findings on this subject was made (Amassian *et al.*, 1989*b*). Subsequently, accounts of paraesthesias in subjects at the National Hospital for Nervous Diseases, Queen Square, became known to the New York group. Thus, paraesthesias elicited by individual MC pulses, although rare, were not unique. The following account is based on collaborative experiments at the above 2 institutions.

METHODS

Human subjects

The series included 3 males and 1 female subject, 2 living in New York and 2 in London. They are identified as subjects 1, 2, 3, 4 in order of ease of eliciting the paraesthesias and their extent. Their ages ranged from 32 to 56 yrs and all were in good health. All subjects were either clinical neurologists or neurophysiologists, were fully informed as to the purpose and procedures of the experiments and co-authored this report. They suffered no mishaps from the experiments.

MC stimulation

In the experiments in New York, the Cadwell MES-10 stimulator was used. Except for the first experiment on subject 1, the small figure '8' MC was used, each half-coil of which measured 5×4.8 cm. The larger, double square MC, each half-coil 7×7 cm was used in the initial motor mapping of subject 1. These MCs are illustrated in Fig. 1 of Amassian *et al.*, 1989*a* and Levy *et al.*, 1990, respectively. Both double coil configurations were shown to induce a current in a pick up wire under the junction region more than 2.5× that under either lateral portion. When tangentially applied to the scalp, their focality of stimulation of motor cortex under the junction region of the half-coils is evidenced in the above publications and below. A more useful measure of the focality of the figure 8 MC is provided by measuring the electric field it induces in an isotropic, unrestricted saline volume conductor (Maccabee *et al.*, 1990). Figure 1 shows the sharp profile of the induced electric field in the XY plane situated 0.5 cm distant from the figure 8 MC, which tangentially orientated (flat) to the volume conductor. The peak electric field was under the junction region and was reduced to one-half at 2 cm and to one-sixth at 3 cm.

The marked reduction of the peak intensity of the electric field at a distance of 3 cm in the volume conductor model implies that excitation occurs superficial to this depth, i.e. in cerebral cortex, or immediately below. Using MCs of different size, Epstein *et al.* (1990) came to the same conclusion. The rostro-caudal and medio-lateral extents of the excitation would be expected to be functions of the stimulus intensity and cannot readily be estimated except by physiological criteria. Thus, when the scalp fields of individual motor units in extensor digitorum communis or indicis proprius are determined with the junction region aligned in the rostro-caudal axis, moving the junction 1 cm either medially or laterally from the optimum often resulted in loss of the response (Amassian *et al.* 1991). While providing evidence for the rapid attenuation of excitation lateral to the junction region, other data are required to estimate that in the axis of the junction (*see below*).

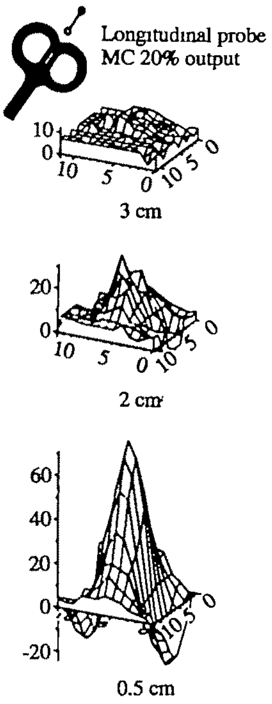

FIG. 1. Electric field induced at various depths in an isotonic saline volume conductor by a figure 8 MC. The bipolar probe is orientated parallel to the junction region of the MC and is manipulated in XY space at distances of 0.5, 2 and 3 cm above the MC, which is tangentially applied to the flat boundary of the volume conductor. The recording interpolar distance is 1 cm. The dimensions of the trough are 33×23×5 cm. The electric field intensity is indicated on the vertical (Z) axis in mV/mm; X and Y axes in cm. (Figure modified from Maccabee *et al.*, 1990.)

In the experiments in London, the Novametrix stimulator was used, energizing either a large round MC (14 cm diameter) or a small round MC (6.5 cm diameter). A tangential orientation of the small round MC was used on subject 2 in one mapping session, but was abandoned because of the difficulty of limiting the site of excitation, which could have been anywhere under the windings. Therefore, edge stimulation with both the small and the larger round MCs were used because this orientation was previously shown with the Cadwell Laboratories round MC to excite motor cortex focally (Amassian *et al.*, 1989*c*). However, the windings in the large Novametrics coil are spread over a considerable width; its effectiveness in edge stimulation is reduced, as shown by weak stimulation of the ulnar nerve at the elbow when the MC is orthogonally orientated. Thus, as with the Cadwell MC, 100% stimulator output was needed and the MC had to be tilted from the orthogonal edge orientation on the scalp to couple sufficient magnetic flux to the volume conductor (the head) to elicit a response.

Defining the scalp location of the MC

Subject 1 is bald so that Cz was located and marked directly on the scalp with an eye-shadow pencil or felt-tip pen. Similarly, points at 1 or 2 cm intervals were directly marked on the scalp and any intermediate positions between these marks were interpolated by eye. In the other 3 subjects, the hairy scalp made it necessary to cover the head tightly with a cap of white non-stretching, synthetic fabric, which was sufficiently porous to avoid sweating. (A rubber bathing cap was tested, but was less comfortable to wear during the extended period required for mapping.) Numbered marks were made on the cap at 2–2.5 cm intervals. After removal, the cap could be copied, yielding a permanent record of the sites of stimulation.

Recordings

Compound muscle action potentials (CMAPs) were recorded with (EEG) surface disc electrodes placed over the muscles. The CMAPs were conventionally amplified with bandpass 0.8 Hz – 10 kHz (New York) and 8 Hz – 3 kHz (London).

Movements of the digits (New York) were recorded by glueing fluorescent markers onto the tips of the digits, illuminating the markers with UV light and recording the XY coordinates of the markers at 1/60 intervals with a TV-computer system. An output of the stored XY coordinates of each marker, i.e. the tip of each digit, could be obtained as a scatter plot immediately after the run or the X and Y components of the movement vector of each digit could later be plotted separately as a function of time.

RESULTS

Subjective quality of the projected sensation

Given their occupations, all 4 subjects clearly were aware of the distinction between paraesthesias, sense of movement and touch sensations. All 4 subjects described the paraesthesias as 'tingling'. Initially, subject 1 likened the tingling to the effect of a brief (100 μs) electric stimulus applied to a digital nerve; subsequently, he described the tingle as lasting longer than the effect of an electric stimulus. However, subject 4 considered the effect of an electric stimulus to the digit a fair description of the MC elicited sensation. In subject 1, repeated MC stimulation resulted first in an increased threshold to elicit the paraesthesias (e.g. requiring 75% of maximum output) and then a loss of paraesthesias. By contrast, a sense of movement could still be elicited at moderate stimulator output levels (e.g. 55% of maximum). When the paraesthesias became fatigued to stimulation on one side of the head, they could still be elicited contralateral to stimulation of the other side.

Subjects 1 and 2 described other sensations including a feeling of movement, or of pulling on a tendon, or in a tendon. These sensations were reported by subject 2 in the absence of CMAP responses in relaxed muscles of the hand, including abductor digiti minimi (ADM) and the first dorsal interosseous (FDI), forearm (flexor and extensors of the digits), upper arm (biceps and triceps) and shoulder (deltoid). However, none of the subjects were stimulated after ischaemically blocking muscle responses in distal arm (*cf* Amassian *et al.*, 1989*a*).

Uniquely, subject 2 described a sensation of light touch of the digits with MC stimulation at certain sites.

Peripheral sites of projected paraesthesias

In all 4 subjects, the sites of projected paraesthesias in the contralateral arm differed among them, tending to be characteristic of the individual. Nevertheless, in all, the paraesthesias were projected to *superficial* sites in the *hand*, usually to the tips of digits. Elsewhere in the hand, the paraesthesias were felt at either the palmar or the dorsal surfaces, either at the ulnar or radial borders and least often in the web between digits.

Subject 1 was stimulated in 5 sessions over a period of 11 mths. Regardless of whether the pre- and post-central regions were mapped with the double square MC or the (smaller) figure 8 MC, the paraesthesias were felt in digit V and IV, or in these among other digits. The other subjects were not stimulated sufficiently often under the same conditions to determine whether their sites of projected paraesthesias were as consistent as in subject 1. In subject 2, the commonest projection sites were, in decreasing order, digit III, IV, II and I. In subject 3, the tingling was felt in digit III and neighbouring digits. In subject 4, the paraesthesias were restricted to the radial border of digit III.

The cortical source of MC induced paraesthesias

A major question is whether paraesthesias elicited by single transcranial pulses reflect the *initial* activation of post-central gyrus, the site long ago implicated when surgically exposed cerebral cortex was repetitively stimulated electrically. To answer this question, the information needed includes: (1) the relation of the point on the figure 8 MC used to define its site on the scalp to where optimal stimulation occurs; (2) the relation of the effective scalp sites to surface landmarks, such as Cz and the inter-aural line and the relation of these landmarks to underlying gyri and sulci.

First, maximal excitation of cerebral cortex would be expected close to the junction region of the 2 half-coils (*see* Methods). Secondly, the locations of gyri and sulci relative to surface landmarks are variable (Homan *et al.*, 1987). Furthermore, the somatosensory and motor representation of the digits approximate one another at the central sulcus, which makes a decision between post-central versus pre-central gyrus especially tenuous if based on surface criteria. However, the threshold for eliciting contralateral movements has long been known to be lower in pre-central as compared with post-central gyrus (e.g. Libet *et al.*, 1964). Therefore, a criterion based on comparing sites that yielded low threshold movement and those yielding paraesthesias seemed to offer the most reliable method of localizing the source of the paraesthesias.

In repeated sessions with subject 1, the paraesthesias could be elicited unaccompanied by either visible or TV-computer tracked movements or EMG responses in ADM, a muscle closely related to the site of the paraesthesias. However, when the MC stimuli were given while this subject contracted his hand muscles, sites yielding the strongest and most widespread paraesthesias either coincided with, or lay *anterior* to those eliciting CMAPs in ADM. In Fig. 2, the junction region of the figure 8 MC was oriented horizontally with the handle pointing posteriorly. Opposite the handle, the point of divergence of the half coils was located at the sites indicated on a line 5 cm lateral to the midline. Paraesthesias were most prominent to stimulation 0.5 cm anterior to the inter-aural line and at still more anterior sites. Because the largest ADM responses were recorded at +0.5, the cortical area excited there presumably lay in pre-central gyrus. Although the background (voluntary) activity was reduced during stimulation more

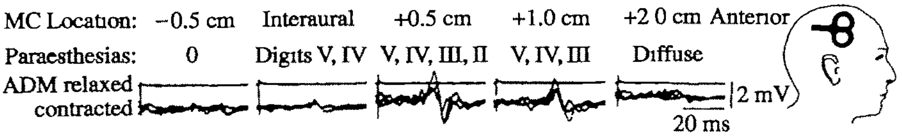

FIG. 2. In subject 1, scalp sites are compared where the figure 8 MC elicits paraesthesias and motor responses. The MC junction region is oriented in the antero-posterior axis 5 cm lateral to the midline, with the handle posterior (*right*). *Top*, the MC location is measured from the point of divergence of the half coils at the end away from the handle. With this orientation of the MC, the midpoint of the junction is anatomically 2.5 cm posterior to the point used for measurement Stimulation throughout was 70% of maximum output of the Cadwell MES-10. *Middle*, sites of paraesthesias indicated with the subject relaxed, 'diffuse' refers to paraesthesias in all digits and part of hand *Bottom pair*, ADM CMAPs when subject is relaxed (*above*) and voluntarily contracting (*below*), respectively (Modified from Amassian *et al.*, 1989*b*.)

posteriorly at the inter-aural line, a small ADM response is visible. Even at −0.5 cm, although the presence of an ADM response is equivocal, movement of digit V was observed, suggesting activation of another muscle. Anteriorly at +2.0 cm, the paraesthesias were diffuse, involving all digits. These findings evidence the spatial resolution feasible in the axis of the junction of the figure 8 MC, movement of as little as 0.5 cm altering the responses.

Over 3 wks later, the mapping was repeated with the junction region of the figure 8 MC pointing in the medio-lateral axis. On an antero-posterior line 5 cm lateral to the midline, the strongest paraesthesias again occurred at, or anterior to sites yielding the largest CMAPs in the voluntarily contracted ADM (Fig. 3).

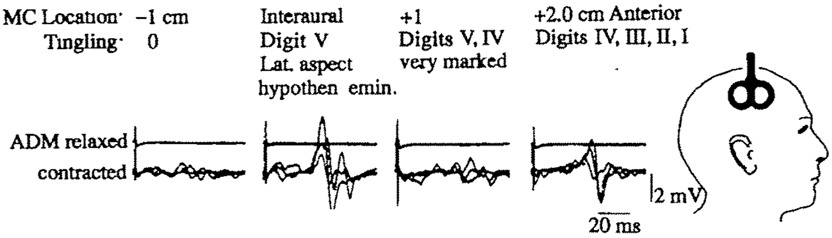

FIG. 3. In subject 1 3 wks later, sites are compared where the figure 8 MC in a different orientation elicits paraesthesias and motor responses. The MC junction region is oriented in the medio-lateral axis, with the point of divergence of the half-coils 3 cm lateral to the midline (*right*). Stimulator output throughout was 66% of maximum Other details as in Fig. 2

Mapping the motor area bilaterally with the (larger) double square MC and just suprathreshold stimuli disclosed the largest motor responses in digit III (Fig. 4). (We previously found that the largest motor responses to focally mapping the motor area differed among individuals, the index finger usually yielding the best, Amassian *et al.*, 1989*c*). In Fig. 4, at the MC stimulus intensity used (60% of maximum output), no responses in digit V were elicited and only very small responses in digit IV. By contrast, this MC elicited paraesthesias most prominently in digits IV and V. Thus, there was a discrepancy between the scalp sites eliciting optimum motor responses and paraesthesias.

In subject 2, the MCs were energized at 100% stimulator output and tilted sufficiently from the orthogonal position to elicit a sensory without or with a motor response. The map of sensory responses is shown in Fig. 5 (*top*). Paraesthesias (tingling) and light touch which were elicited in approximately equal numbers at sites predominantly anterior to the inter-aural line. Given that the round MCs were tilted anterior to the inter-aural line, the magnetic flux was mainly directed anteriorly, with peak excitation occurring close to, but anterior to the site of the contacting edge. Significantly, movements were elicited in either relaxed or contracting muscle predominantly at, or even posterior (sites 8, 2, 25) to those yielding paraesthesias. As in subject 1, movements could occur in digits remote from the site of paraesthesias; e.g. at site 19, paraesthesias were elicited along the radial border of digit IV, but during voluntary contraction, movement was greater in digit II than III.

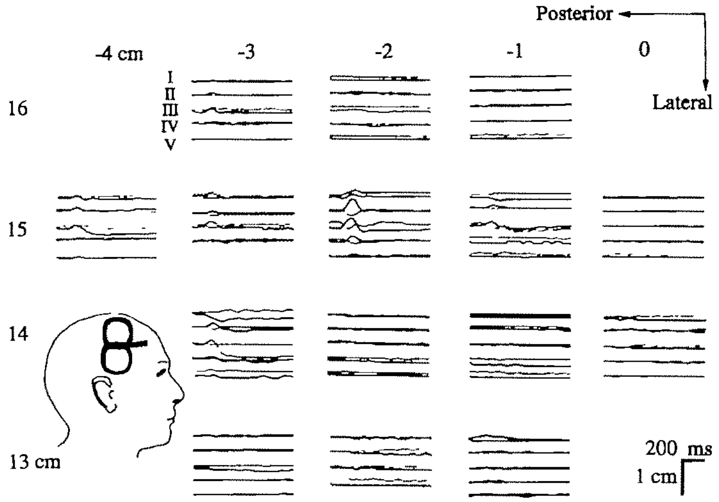

FIG. 4. In subject 1 with relaxed muscles, typical digit movements elicited by stimulating different scalp sites with the double square MC The MC junction region was orientated in the antero-posterior axis with the handle anterior (*bottom left*). Stimulator output throughout was 60%. The X axis (thick line) and Y axis (thin line) components of the movement vectors of digits I-V are displayed as a function of time. With this MC, midpoint of the junction region is anatomically 3 5 cm anterior to the point used for measurement of MC position, which is the point of divergence of the half-coils on the side away from the handle. The antero-posterior coordinate is measured from Cz and the latero-medial coordinate from the external auditory meatus The 1 cm calibration (*bottom right*) applies to the digit movements.

The thresholds for eliciting paraesthesias and muscle activation were conveniently compared by progressively tilting anteriorly the large round MC, with the edge contacting sites (15) or between sites (9 and 16). At both sites, tingling was elicited without activation of relaxed muscle; voluntary contraction during stimulation at site 15 revealed a small CMAP in FDI (Fig. 6).

By contrast, when the larger round MC was tilted posteriorly, presumably exciting cortex posterior to the contacting edge of the MC, paraesthesias were elicited at only one site (21) in the ulnar border of digit I. A sense of tendon movement on the ulnar aspect was elicited at site 8 and light touch in digits I and V, which were accompanied by CMAPs in ADM and the extensors in the forearm.

Subject 3 differed from subjects 1 and 2 in that the threshold for paraesthesias exceeded that for eliciting movement in the relaxed hand. When the round MC was mid-tilted anteriorly, with the contacting edge 5.2 cm lateral in the inter-aural line (site A), neither sensation nor movement were elicited in the relaxed hand. When the MC was shifted 0.8 cm anteriorly (site B), movements without sensation were elicited. A similar shift anteriorly (site C) increased the movement and elicited sensations. Stimulating at site A with increasing tilts (1–4) resulted in progressively increasing muscle responses, with paraesthesias initially in digits III and IV at tilt 3, increasing in IV and V at tilt 4, which was almost tangential. Moving medially resulted in a shift of paraesthesias from digits II and III to III and IV.

In subject 4, although the most prominent motor responses were in digit II, the rather faint paraesthesias were felt along the radial border of digit III. As in the other 3 subjects, the paraesthesias were elicited best from scalp sites that could also elicit movement.

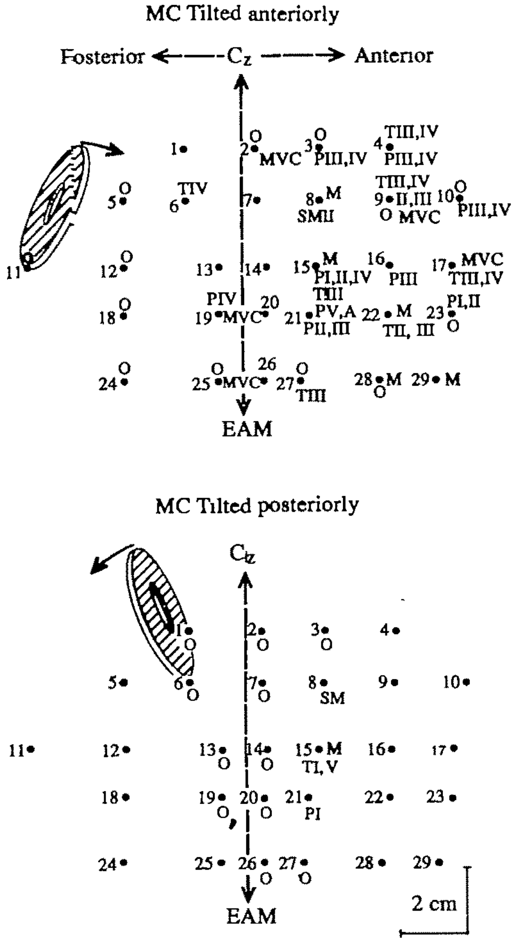

FIG. 5. In subject 2, sensations and motor responses elicited by large and small round MCs are mapped with anterior (*above*) and posterior tilts (*below*). The middle of the contacting edge of the MC at each scalp site is indicated by a dot, which is numbered at its left, the sensory responses to the small and large round MCs are indicated above and below, respectively, and motor responses are indicated to the right of the dot. Appreviations: EAM = external auditory meatus; A = arm, P = paraesthesias; T = touch; SM = sense of movement or sensation in tendon, M = motor responses in relaxed muscle; MVC = motor responses in voluntarily contracted muscle Differing responses to stimulation with a given MC at the same site are listed below one another.

Characteristics of the motor response

In all 4 subjects, any movement resulting from the individual MC pulses resembled the brief, twitch-like contractions recorded from subjects never reporting paraesthesias. The EMGs recorded in subjects 1, 2 and 3 also appeared normal in appearance, showing no evidence of a second wave, much less after-discharge. We conclude that the unusual sensations experienced by the 4 subjects were unaccompanied by any unusual feature of motor responses elicited from identical sites in motor cortex.

Interaction of paraesthesias and peripheral stimulation

The paraesthesias were experienced very soon after the MC pulse was delivered. Subject 2 reported they were felt when the 'click' of the energized MC was heard. However, only in subject 1 were the paraesthesias considered sufficiently localized and reproducible to warrant studying the interaction of transcranial and peripheral stimuli. The figure 8 MC was positioned with the junction region in the antero-posterior axis, with the handle end directed anteriorly and the medial half-coil conforming to the skull

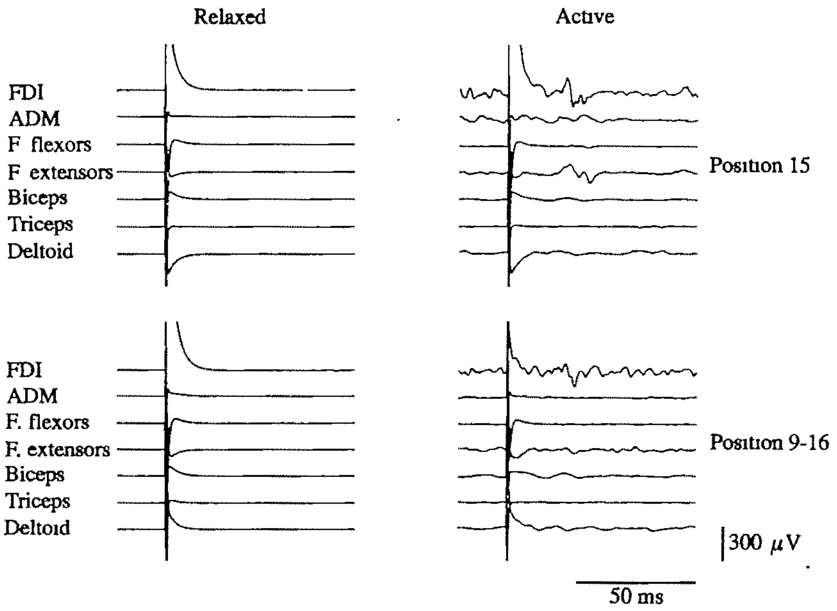

FIG. 6 In subject 2, motor responses in relaxed and voluntarily contracted muscle with the large round MC tilted enough anteriorly to elicit paraesthesias

curvature. When the MC was energized at 60% of maximum stimulator output, tingling was felt reproducibly in contralateral digit V. Digits I and V ipsilateral to the paraesthesias were stimulated electrically with individual 100 μs rectangular pulses through ring electrodes. The intervals between MC stimulus and digit I electrical stimulus and between digit V and digit I electrical stimuli were varied and the sequence of stimuli reversed. Subject 1 was required to identify which digit was first stimulated and whether the lead time over the second stimulus was large or small. Failure to perceive any difference in timing of the stimuli constituted an additional category of response. When both stimuli were given to the digits, the period when no difference in timing was perceived was approximately symmetrical around 0 time, i.e. when the stimuli to the digits were synchronous (Fig. 7, *top*). The transition from failing to perceive the sequence to correctly perceiving it occurred at interstimulus intervals between 50 and 63 ms, averaging 56 ms. However, when the peripheral stimulus was paired with a transcranial MC, the reports had increased variability. The corresponding values for the digit I-MC and MC-digit I sequences were 36 ms and 50 ms, respectively (Fig. 7, *bottom*). The overall period of inability to report correctly the sequence markedly reduced (86 ms) when digit and MC stimuli were paired as compared with paired stimuli to the digits (112 ms).

In a subject who never felt paraesthesias to MC stimulation, the hypothesis was tested that peripherally induced paraesthesias might sum with the effect of a transcranial MC stimulus to elicit a stimulus-related increase in the paraesthesias. Paraesthesias were induced in the hand 3 min after occlusion of the blood supply in the upper arm; during this period, motor cortical stimulation with a small oval MC yielded focal motor responses, but no increase in the paraesthesias.

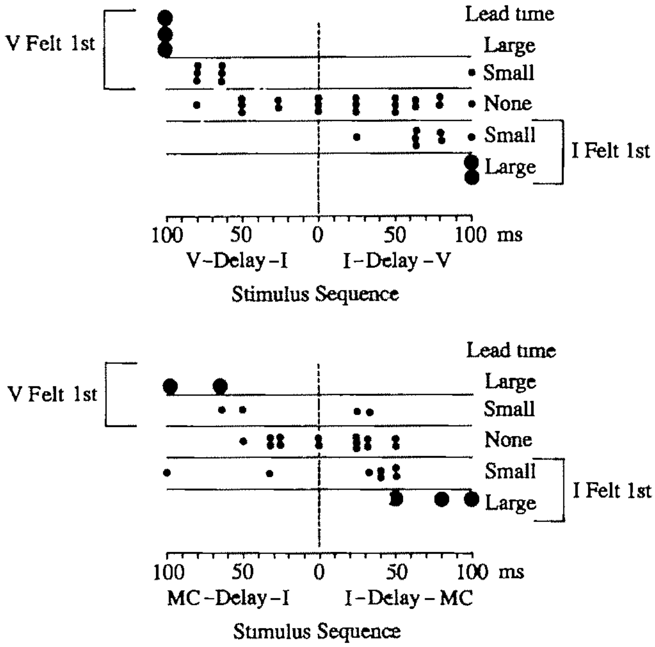

FIG 7. In subject 1, subjective responses to combinations of electrical stimulation of digits and transcranial MC stimulation as a function of interstimulus interval. The subject was required to estimate whether or not the stimuli were separated in time; if the stimuli were separated in time, the first had to be identified and its lead time subjectively judged as 'large' or 'small'. Other details described in text

DISCUSSION

The cortical source of the paraesthesias

In all 4 subjects, focal transcranial stimulation with a dual coil, or with the edge of a round coil, elicited projected paraesthesias from scalp sites similar to or anterior to those yielding movement. However, when the junction region of the Cadwell figure 8 MC lies in the anteroposterior axis as in Fig. 2, given the polyphasic energizing pulse, there is a possibility of several sites of stimulation (Claus *et al.*, 1990); for example, the anterior site could be in motor cortex and the posterior site in parietal lobe. Significantly, the correlation of sites eliciting movements and paraesthesias was still found when the junction was oriented mediolaterally; because the site descriptions were based on the point of divergence of the coils on the far side from the handle, any point of excitation closer to the handle would lie still more *anterior* to the central sulcus, which has an anterolateral trajectory. Furthermore, analogous findings were obtained with the Novametrix round MC when on edge and tilted anteriorly. The correlation between paraesthesias and movement makes it virtually certain that the paraesthesias mostly stem from direct excitation of either motor cortex or neurons projecting there. Whether any other cortical areas serve as sources for the paraesthesias is less clear. For example, in subject 2, paraesthesias were elicited in digits III and IV from a site (10) at least 4.1 cm anterior to a site (8) yielding movement in the relaxed hand. Because the round MC was tilted anteriorly, the site of cortical excitation could have been still more anterior. Most likely therefore, area 6 can also be a source of paraesthesias. Paraesthesias in digits I and II were elicited from a site (23) even more anterior (7.2 cm) to a site (19) yielding movement in the relaxed hand. Although thumb movements can be elicited by stimulation anteriorly in the pre-central gyrus (fig. 12 in Penfield and Boldrey, 1937; Scarff, 1940), site (23) would appear to be further anterior, in area 6. Concerning the parietal lobe, the only possible source of the paraesthesias is a region sufficiently close to the central sulcus to yield movement from current spread to the adjoining motor cortex. Because tilting the round MC *posteriorly* failed to elicit paraesthesias from sites that yielded them when the tilt was anterior, it seems unlikely that even post-central cortex (Brodmann area 3) adjoining the motor cortex is a source of MC induced paraesthesias.

The topography of the digit representation of the projected paraesthesias is complex. Only to a minor extent do the data fit the conventional homunculus pattern of representations in pre- and post-central gyri (fig. 26 in Penfield and Boldrey, 1937). Thus, in subject 3 the expected shift of digit representation towards the ulnar aspect of the hand occurred when the MC stimulation was directed more medially. In subject 2, digits I and II tended to have a better representation lateral to the representation of digit IV, but exceptions to a simple topographical pattern were striking. The most detailed map of digit movements given by Penfield and Boldrey (1937) in their fig. 12, shows extraordinary departures from the conventional sequence I to V medially. A muscle can have multiple *separated* representations in motor cortex of primates (Strick and Preston, 1978); by analogy, a similar pattern of representation of paraesthesias may occur. An increased sensitivity (*see below*) of the perceptual system to inputs from certain sites within motor cortex would further complicate mapping studies.

Repeatedly, paraesthesias were projected to sites other than those exhibiting the predominant motor response to the MC stimulus. Because short-latency responses in hand muscles (Felix and Wiesendanger, 1971) are subserved by the corticospinal system, it seems unlikely that the paraesthesias are mediated by collaterals of corticospinal neurons. Whether the paraesthesias stem from orthodromic excitation of motor cortical projections, or from antidromic excitation of neurons projecting to motor cortex (with excitation distributed through their collaterals) cannot be identified from our data. However, connections between motor cortex and subcortical nuclei, or other cortical areas such as parietal lobe or supplementary motor area (Pandya and Kuypers, 1969), are usually reciprocal so that the issue of orthodromic versus antidromic excitation may not be crucial for localization.

In discussing possible subcortical substrata for the central sense of movement (Amassian *et al.*, 1989*a*), we emphasized the possible role of excitatory connections with conventional somatosensory nuclei, such as thalamic n. VPL (Tsumoto *et al.*, 1975) and the dorsal column nuclei (Jabbur and Towe, 1961). However, the thalamic intralaminar nuclei, n. centralis lateralis, centrum medianum and n. parafascicularis to a small extent, also receive input from motor cortex (DeVito, 1969; Petras, 1972; Miyata and Sasaki, 1983); n. centrum medianum and parafascicularis mainly receive input from area 6. Although intralaminar nuclei project to motor cortex (Kievit and Kuypers, 1975, 1977), the projection from n. centrum medianum is much less massive than the input from motor cortex, providing a significant exception to the general reciprocity of connections between cortical and subcortical nuclei. A role of the intralaminar nuclei in pain perception in humans (Mark *et al.*, 1963) and nociception in animals (Albe-Fessard and Kruger, 1962) is well established. Their possible role in the sensations elicited by MC stimulation of motor cortex is suggested by the findings in a patient with intractable pain, who experienced pins and needles in the left arm and leg when stimulated electrically at 100 Hz through implanted electrodes near thalamic

n. parafascicularis (Mark *et al.*, 1963). A subsequent radio-frequency lesion made through these electrodes destroyed n. parafascicularis and most of n. centrum medianum and relieved the pain. In another patient, repetitive electrical stimulation near n. centrum medianum elicited an 'unpleasant feeling', implying again that activation of certain intralaminar nuclei can reach consciousness.

The subjective quality of the paraesthesias

Tingling is commonly felt by patients whose exposed post-central gyrus is repetitively stimulated electrically. The somatosensory submodalities, e.g. touch, pressure or brushing of hairs are not reported, or rarely so, although the post-central gyrus is irreplacable in fine mechanoreceptive sensibility (Corkin *et al.*, 1970). The unphysiological nature of the post-central stimulation presumably accounts for the report of paraesthesias. Because the exposed crown of the post-central gyrus is stimulated at operation, a report of tingling may reflect the unphysiological stimulation of cortex normally subserving light mechanoreceptive *cutaneous* function (Brodmann's area 1) rather than deeper joint and muscle proprioceptive functions of Brodmann's areas 2 and 3a (Kaas *et al.*, 1979). Although derived from motor cortex, the findings in subject 2 support the notion that tingling is related to light contact sensibility. In subject 2, neighbouring sites might elicit either tingling or touch; indeed the same site could yield either sensation on different occasions.

A tetanic train of stimuli is the adequate stimulus for the post-central gyrus (Libet *et al.*, 1964). By contrast, a *single* MC stimulus to motor cortex produces centrally a sense of movement (Amassian *et al.*, 1989*a*) and other sensations in a subgroup of adult humans, the 4 subjects in this report. The difference between stimulation of these 2 gyri is unlikely to reflect the uniqueness of brief high frequency discharge by pre-central corticospinal neurons to a single electrical (Patton and Amassian, 1954; Kernell and Wu, 1967; Rosenthal *et al.*, 1967) or MC stimulus (Amassian *et al.*, 1990*b*). Presumably, post-central neurons also have electrically excitable components and excitable presynaptic inputs. The crucial difference appears to be that motor cortex accesses the 'perceptual system' with a much briefer discharge than is required from post-central cortex. The difference may reflect the special role of post-central gyrus in conscious, mechanoreceptive discrimination, a behavioural function perhaps requiring analysis extended in time. By contrast, motor cortex presumably requires internal feedback (corollary discharge; reviewed in Goodwin *et al.*, 1972 and McCloskey *et al.*, 1983) in time to correct fast finger movements. If such internal feedback required discharges lasting several hundred milliseconds to represent each state, the execution of rapid skilled movements would be severely limited. The utility of such feedback is not restricted to 'proprioceptive' type corollary discharge. Cutaneous corollary type discharge would also be valuable in guiding finger movements.

Distinguishing between sequential MC and peripheral stimuli

Substituting an MC stimulus for one of a dual peripheral stimulus sequence led to a result that was unexpected from the simple model shown in Fig. 8. An electrical stimulus to each of 2 digits elicits a transynaptic response in pre- and post-central gyri approximately 20 ms later. No later than and probably significantly earlier than 500 ms afterwards, the subject perceives the stimulus (the figure 500 ms, i.e. their parametric region A, is taken from Libet *et al.*, 1964, but its exact value is immaterial for the discussion below). When the second stimulus to another digit is given 56 ms later, the sequence

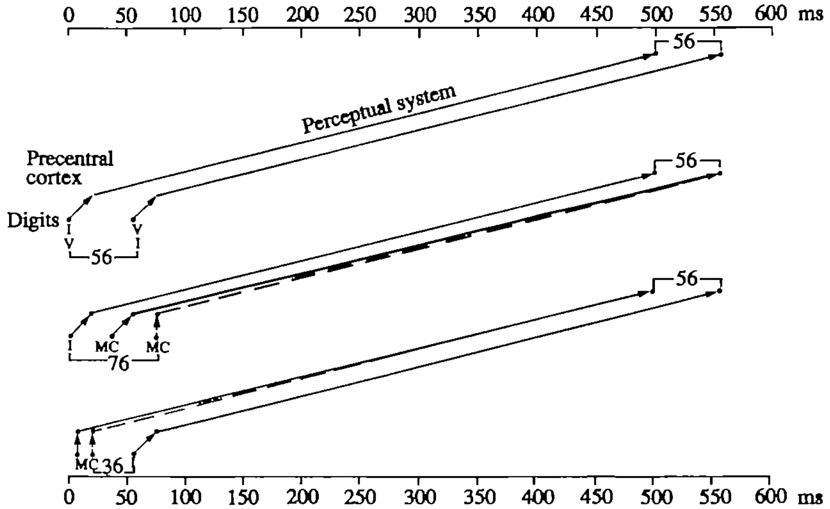
0 50 100 150 200 250 300 350 400 450 500 550 600 ms
56
Perceptual system
Precentral cortex
Digits
I
V
V
I
56
56
I
MC
MC
76
56
MC
36
0 50 100 150 200 250 300 350 400 450 500 550 600 ms

FIG. 8. Diagram comparing expected (interrupted line) and observed (continuous line) effects on sensation of combined transcranial MC and electrical digit stimulation. *Top*, it is assumed that the interstimulus delay of 56 ms is represented by some function of 56 ms in the perceptual system. Although for simplicity an equal value (56 ms) in the perceptual system is assigned in the diagram, the absolute value is immaterial provided that it is increased (*middle*), or reduced (*bottom*) by the effect of conduction delay from digit to motor cortex. The expected interstimulus intervals are indicated below the corresponding stimulus combinations Other details described in text.

commences to be correctly perceived (*top diagram*). Although transmission and perception of the second response may be slowed, this is disregarded in the simplified diagram. According to the model, if the first stimulus is a transcranial MC pulse (*bottom diagram*), 20 ms should be *saved* in transmission of the first response, i.e. a digital stimulus given (56−20) = 36 ms later should just be distinguishable from the first. Experimentally, the interstimulus interval was approximately 50 ms. The trivial disagreement between the model and the data suggests that the processing delay in the perceptual system is not significantly greater for MC induced paraesthesias than for peripheral input (*cf* Libet *et al.*, 1964). (The validity of this conclusion is not tied to the particular model illustrated in Fig. 8.) By contrast, the sequence digit stimulus/MC stimulus would theoretically require an *increased* interstimulus interval (56+20) = 76 ms (*middle diagram*). Experimentally, a *reduced* interval (36 ms) was found, which implies slowed perceptual processing of the response to the MC pulse when it *follows* a peripheral stimulus. Given the fatiguability of paraesthesias in this subject, the possibility that a digit stimulus, which is perceived with less fatigue, might partially inhibit the less robust paraesthesias seems plausible. Finally, we must emphasize that in only one subject were the paraesthesias reproducible enough to warrant interacting digital and transcranial stimuli.

Incidence of subjects reporting paraesthesia

Subjects reporting paraesthesias after single MC pulses are clearly in the minority. Our impression is that the incidence is of the order of 20−30% of normal subjects. Possible explanations for the phenomenon in this minority of adults include: (1) the single MC pulse elicits a prolonged (e.g. 500 ms) repetitive discharge in cortical neurons mimicking the electrical trains effective on exposed post-central cortex. Significantly, the motor responses to the MC pulse in all 4 subjects were indistinguishable from those who never reported paraesthesias; this negative finding implies that large corticospinal neurons in the 4 subjects lacked any unusual properties. However, other pyramidal neurons situated in other laminar and with targets other than motor neurons might give prolonged repetitive discharges. Such discharging foci would not necessarily be excluded by negative findings in the EEG and might be hard to identify. Weighing against a prolonged repetitive discharge by a subclass of motor cortical neurons as a requirement for the excitation to be expressed as paraesthesias is the finding that single MC pulses normally elicit *centrally* a sense of movement (Amassian *et al.*, 1989*a*). In cats and monkeys, a single electrical pulse (Patton and Amassian 1954; Kernell and Wu 1967; Rosenthal *et al.*, 1967) and in monkeys, a single MC pulse (Amassian *et al.*, 1990*b*) elicit only a very brief high frequency discharge by corticospinal neurons, lasting less than 10 ms. The discontinuous jumps in latency of response by motor units driven by transcranial MC stimulation (Rothwell *et al.*, 1987; Amassian *et al.*, 1989*c*; Day *et al.*, 1989) place similar limits on the duration of the high frequency response in humans. Therefore, no *a priori* reason is required for repetitive discharge by motor cortical neurons to be abnormally prolonged in subserving paraesthesias. (2) The explanation remaining for the paraesthesias is that the perceptual system has an increased sensitivity to the motor cortical discharge elicited by the MC. As yet we have not devised a test of this hypothesis. As a first step, it would be of interest to determine if subjects not normally reporting paraesthesias could do so under hypnosis, or during hyperventilation, or during sensory isolation, or during insulin-induced hypoglycaemia, or after administration of hallucinogens or naloxone. If indeed the paraesthesias reflect a heightened sensitivity to motor cortical input, then increasing the threshold of the perceptual system by small doses of narcotics or diazopenes might abolish the phenomenon, while leaving intact the central sense of movement. It seems clear that additional approaches are needed to further understanding of the unusual experience of central paraesthesia.

REFERENCES

ALBE-FESSARD D, KRUGER L (1962) Duality of unit discharges from cat centrum medianum in response to natural and electrical stimulation. *Journal of Neurophysiology*, **25**, 3–20.

AMASSIAN VE, CRACCO RQ, MACCABEE PJ (1989*a*) A sense of movement elicited in paralyzed distal arm by focal magnetic coil stimulation of human motor cortex. *Brain Research, Amsterdam*, **479**, 355–360.

AMASSIAN VE, CRACCO RQ, MACCABEE PJ, SOMASUNDARAM M (1989*b*) Focal magnetic coil stimulation near human central sulcus exceptionally elicits localized contralateral paraesthesias. *Journal of Physiology, London*, **414**, 22*P*.

AMASSIAN VE, CRACCO RQ, MACCABEE PJ (1989*c*) Focal stimulation of human cerebral cortex with the magnetic coil: a comparison with electrical stimulation. *Electroencephalography and Clinical Neurophysiology*, **74**, 401–416.

AMASSIAN VE, MACCABEE PJ, CRACCO RQ, CRACCO JB, RUDELL AP, EBERLE L (1990*a*) A short magnetic pulse train to human occipital cortex prolongs visual suppression. *Journal of Physiology, London*, **430**, 109*P*.

AMASSIAN VE, QUIRK GJ, STEWART M (1990*b*) A comparison of corticospinal activation by magnetic coil and electrical stimulation of monkey motor cortex. *Electroencephalography and Clinical Neurophysiology*, **77**, 390–401.

AMASSIAN VE, CRACCO RQ, MACCABEE PJ, BIGLAND-RITCHIE B, CRACCO JB (1991) Magnetic coil matching focal and non-focal magnetic coil stimulation to properties of human nervous system: mapping motor unit fields in motor cortex contrasted with altering sequential digit movements by premotor-SMA stimulation. *Electroencephalography and Clinical Neurophysiology*, Supplement, **43**, 3–28.

BARKER AT, FREESTON IL, JALINOUS R, MERTON PA, MORTON HB (1985) Magnetic stimulation of the human brain. *Journal of Physiology, London*, **369**, *3P*.

BARKER AT, FREESTON IL, JALINOUS R, JARRATT JA (1987) Magnetic stimulation of the human brain and peripheral nervous system: an introduction and the results of an initial clinical evaluation. *Neurosurgery*, **20**, 100–109.

CLAUS D, MURRAY NMF, SPITZER A, FLÜGEL D (1990) The influence of stimulus type on the magnetic excitation of nerve structures *Electroencephalography and Clinical Neurophysiology*, **75**, 342–349.

CORKIN S, MILNER B, RASMUSSEN T (1970) Somatosensory thresholds: contrasting effects of postcentral-gyrus and posterior parietal-lobe excisions. *Archives of Neurology, Chicago*, **23**, 41–58.

DAY BL, DRESSLER D, MAERTENS DE NOORDHOUT A, MARSDEN CD, NAKASHIMA K, ROTHWELL JC *et al.* (1989) Electric and magnetic stimulation of human motor cortex: surface EMG and single motor unit responses. *Journal of Physiology, London*, **412**, 449–473.

DEVITO JL (1969) Projections from the cerebral cortex to intralaminar nuclei in monkey. *Journal of Comparative Neurology*, **136**, 193–201.

EPSTEIN CM, SCHWARTZBERG DG, DAVEY KR, SUDDERTH DB (1990) Localizing the site of magnetic brain stimulation in humans. *Neurology, Cleveland*, **40**, 666–670.

FELIX D, WIESENDANGER M (1971) Pyramidal and non-pyramidal motor cortical effects on distal forelimb muscles of monkeys. *Experimental Brain Research*, **12**, 81–91.

FOERSTER O (1936) The motor cortex in man in the light of Hughlings Jackson's doctrines. *Brain*, **59**, 135–159.

GOODWIN GW, MCCLOSKEY DI, MATTHEWS PBC (1972) The contribution of muscle afferents to kinaesthesia shown by vibration induced illusions of movement and by the effects of paralysing joint afferents. *Brain*, **95**, 705–748.

HOMAN RW, HERMAN J, PURDY P (1987) Cerebral location of international 10-20 system electrode placement. *Electroencephalography and Clinical Neurophysiology*, **66**, 376–382.

JABBUR SJ, TOWE AL (1961) Cortical excitation of neurons in dorsal column nuclei of cat, including an analysis of pathways. *Journal of Neurophysiology*, **24**, 499–509.

KAAS JH, NELSON RJ, SUR M, LIN C-S, MERZENICH MM (1979) Multiple representations of the body within the primary somatosensory cortex of primates. *Science*, **204**, 521–523.

KERNELL D, WU C-P (1967) Responses of the pyramidal tract to stimulation of the baboon's motor cortex. *Journal of Physiology, London*, **191**, 653–672.

KIEVIT J, KUYPERS HGJM (1975) Subcortical afferents to the frontal lobe in the rhesus monkey studied by means of retrograde horseradish peroxidase transport. *Brain Research, Amsterdam*, **85**, 261–266.

KIEVIT J, KUYPERS HGJM (1977) Organization of the thalamo-cortical connexions to the frontal lobe in the rhesus monkey. *Experimental Brain Research*, **29**, 299–322.

LEVY WJ, AMASSIAN VE, TRAAD M, CADWELL J (1990) Focal magnetic coil stimulation reveals motor cortical system reorganized in humans after traumatic quadriplegia. *Brain Research, Amsterdam*, **510**, 130–134.

LIBET B, ALBERTS WW, WRIGHT EW, DELATTRE LD, LEVIN G, FEINSTEIN B (1964) Production of threshold levels of conscious sensation by electrical stimulation of human somatosensory cortex. *Journal of Neurophysiology*, **27**, 546–578.

MACCABEE PJ, EBERLE L, AMASSIAN VE, CRACCO RQ, RUDELL A, JAYACHANDRA M (1990) Spatial distribution of the electric field induced in volume by round and figure '8' magnetic coils: relevance to activation of sensory nerve fibers. *Electroencephalography and Clinical Neurophysiology*, **76**, 131–141.

MCCLOSKEY DI, COLEBATCH JG, POTTER EK, BURKE D (1983) Judgements about onset of rapid voluntary movements in man. *Journal of Neurophysiology*, **49**, 851–863.

MARK VH, ERVIN FR, YAKOVLEV PI (1963) Stereotactic thalamotomy: III. The verification of anatomical lesion sites in the human thalamus. *Archives of Neurology, Chicago*, **8**, 528–538.

MIYATA M, SASAKI K (1983) HRP studies on thalamocortical neurons related to the cerebellocerebral projection in the monkey. *Brain Research, Amsterdam*, **274**, 213–224.

PANDYA DN, KUYPERS HGJM (1969) Cortico-cortical connections in the rhesus monkey. *Brain Research, Amsterdam*, **13**, 13–36.

PATTON HD, AMASSIAN VE (1954) Single- and multiple-unit analysis of cortical stage of pyramidal tract activation. *Journal of Neurophysiology*, **17**, 345–363.

PENFIELD W, BOLDREY E (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain*, **60**, 389–443.

PETRAS JM (1972) Corticostriate and corticothalamic connections in the chimpanzee. In: *Corticothalamic Projections and Sensorimotor Activities*. Edited by T. L. Frigyesi, E. Rinvik and M. D. Yahr. New York: Raven Press, pp. 201–219.

ROSENTHAL J, WALLER HJ, AMASSIAN VE (1967) An analysis of the activation of motor cortical neurons by surface stimulation. *Journal of Neurophysiology*, **30**, 844–858.

ROTHWELL JC, DAY BL, THOMPSON PD, DICK JPR, MARSDEN CD (1987) Some experiences of techniques for stimulation of the human cerebral motor cortex through the scalp. *Neurosurgery*, **20**, 156–163.

SCARFF JE (1940) Primary cortical centers for movements of upper and lower limbs in man: observations based on electrical stimulation. *Archives of Neurology and Psychiatry, Chicago*, **44**, 243–299.

STRICK PL, PRESTON JB (1978) Multiple representation in the primate motor cortex. *Brain Research*, **154**, 366–370.

TSUMOTO T, NAKAMURA S, IWAMA K (1975) Pyramidal tract control over cutaneous and kinesthetic sensory transmission in the cat thalamus. *Experimental Brain Research*, **22**, 281–294.

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THE DECLINE OF WORKING MEMORY IN ALZHEIMER'S DISEASE

A LONGITUDINAL STUDY

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SUMMARY

A previous study (Baddeley *et al.*, 1986) explored the hypothesis that patients suffering from dementia of the Alzheimer type (AD) are particularly impaired in the functioning of the central executive component of working memory. It showed that, when patients are required to perform 2 concurrent tasks simultaneously, the AD patients are particularly impaired, even when level of performance on the individual tasks is equated with that of age-matched controls. Although the results were clear, interpretation was still complicated by 2 issues: first, the question of comparability of performance on the separate tests between AD and control patients; secondly, the question of whether our results could be interpreted simply in terms of a limited general processing capacity being more taxed by more difficult dual tasks than by the individual tasks performed alone.

The present study followed up the AD and control patients after 6 and 12 mths. We were able to allow for the problem of comparability of performance by using patients as their own control. Under these conditions, there is a very clear tendency for dual task performance to deteriorate while single task performance is maintained. A second experiment varied difficulty within a single task in which patients and controls were required to categorize words as belonging to 1, 2 or 4 semantic categories. There was a clear effect of number of categories on performance and a systematic decline in performance over time. There was, however, no interaction between task difficulty as measured by number of alternatives and rate of deterioration, suggesting that the progressive deterioration in performance shown by AD patients is a function of whether single or dual task performance is required, and is not dependent on simple level of task difficulty.

Implications for the analysis of the central executive component of working memory are discussed.

INTRODUCTION

Impaired memory performance is one of the earliest and most characteristic symptoms of Alzheimer's disease (AD) (McKhann *et al.*, 1984; American Psychiatric Association, 1987; Spinnler and Della Sala, 1988; Wilcock *et al.*, 1989), a symptom that reveals itself both in complaints of lapses of memory in everyday life, and in decrements in the performance of laboratory tasks (Miller, 1977; Wilson *et al.*, 1983; Spinnler *et al.*, 1988). Because the memory deficit is so characteristic, understanding its nature is likely to form an important component of analysing the functional deficit occurring in AD, which in turn may lead to the development of tests which offer early diagnosis.

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The most extensively explored memory deficit is that associated with the amnesic syndrome, the gross impairment in long-term learning that occurs in Korsakoff patients, and in patients with bilateral damage to the temporal lobes, hippocampus and diencephalon (Zangwill, 1946; Milner 1966; Warrington and Weiskrantz, 1970; Butters and Stuss, 1989). Such patients show grossly impaired learning of new material, whether visual or verbal, together with unimpaired short-term memory as measured by digit span or by the recency effect in free recall (Baddeley and Warrington, 1970). The functioning of semantic memory may also be unimpaired, as indicated by retained knowledge of word meanings, and unimpaired speed of access to knowledge of the world, while the capacity to recollect events from well before the onset of the illness may also be relatively normal (Wilson and Baddeley, 1988).

The memory deficit in AD resembles that of the amnesic syndrome in showing a broad impairment in the capacity for new learning, coupled with a relative sparing of the recency effect in free recall (Wilson *et al.*, 1983; Spinnler *et al.*, 1988). The memory deficit in AD is more pervasive than that found in the amnesic syndrome, however, with clear evidence of impairment in access to semantic memory (Chertkow and Bub, 1990) which is typically also accompanied by retrograde amnesia (Kopelman, 1989) and autobiographical amnesia (Dall'Ora *et al.*, 1989). Slowed access to semantic memory and some evidence of retrograde amnesia are, however, not uncommon in any condition where substantial brain damage occurs. Deficits in immediate memory span are shown by AD patients, whether tested verbally using the standard span procedure, or spatially using the Corsi Block Tapping technique (Spinnler *et al.*, 1988).

This deficit of AD patients in short-term or working memory has been explored in some detail (Miller, 1973; Morris, 1984, 1986; Kopelman, 1985). Reviewing this and other data, Morris and Baddeley (1988) suggest that a deficit in the controlling central executive component of working memory may be characteristic of AD patients, and may lie at the root of many of their cognitive processing deficits. A similar position is taken by Becker (1988), who suggests that AD patients suffer from 2 principal deficits, one involving an impairment in new learning similar to that shown in the classic amnesic syndrome, while the other represents a defect in the functioning of the central executive component of working memory. AD patients showing such a dissociation have been reported by Becker himself (1988) and by Baddeley *et al.* (1991).

The concept of working memory was developed by Baddeley and Hitch (1974) to account for the increasingly complex pattern of data from experiments on short-term memory. They proposed that the existing concept of a unitary short-term memory store should be replaced by the assumption of a working memory system comprising a number of sub-components. Three principal sub-systems were identified, namely the central executive, the visuo-spatial scratchpad and the articulatory loop.

The central executive is assumed to be an attentional control system that has access to long-term memory and is served by 2 subsidiary slave systems, the visuo-spatial scratchpad which is assumed to set up and maintain visual images, and the articulatory or phonological loop, which is assumed to be responsible for setting up and maintaining speech-based material. For a number of reasons, the term phonological loop is now preferred (e.g. Baddeley, 1990) and we shall use this term throughout. The model has been successful in accounting for a range of laboratory studies on normal subjects, and has also proved useful in accounting for neuropsychological deficits in brain-damaged patients (for reviews *see* Baddeley, 1986; Vallar and Shallice, 1990).

Baddeley (1986) has suggested that the attentional control model of Norman and Shallice (1980, 1986) might provide a good hypothesis for the way in which the central executive operates. One of the functions of the central executive is to coordinate information from a number of different sources, and as such it is assumed to play a role in many cognitive tasks, including those requiring short-term storage. The assumption of a central executive deficit would therefore account for the impairment in AD patients on tests of short-term memory (Corkin, 1982; Kopelman, 1985; Morris, 1986; Spinnler *et al.*, 1988). This contrasts with the finding that patients with a pure amnesia are able to perform short-term memory tasks very effectively (Baddeley and Warrington, 1970; Warrington, 1982).

While the evidence is broadly consistent with the assumption that AD patients have impaired functioning of the central executive component of working memory, many of the results are open to a more general interpretation which simply assumes that the overall information-processing capacity or efficiency (e.g. Craik, 1984) of patients with AD is reduced. One prediction from this would be that anything that increases the demand placed on the patient will have an exaggerated effect on the performance of the AD group. Baddeley *et al.* (1986) attempted to test the central executive deficit hypothesis. They argued that a central executive deficit should lead to an exaggerated impairment in performance when AD patients are required to coordinate performance simultaneously on 2 different tasks. They attemped to avoid the criticism that the AD patients were being excessively overloaded by adjusting the level of difficulty of the primary task, pursuit tracking, so that the overall performance of patients and controls was equivalent. They then combined this with each of 3 secondary tasks. The first of these involved repeatedly uttering the digits 1 to 5, a task that was assumed to place minimal processing demands on the system, other than the requirement to coordinate it with tracking. The second task involved pressing a foot pedal whenever a sound occurred. The third involved combining tracking with concurrent memory span for digits, where the level of difficulty of the digit task was adjusted to a point at which both AD patients and controls were functioning at an equivalent level, and hence were presumably equally heavily loaded. The tasks of adaptive tracking, articulatory suppression, auditory reaction time and digit span were selected so as to minimize the amount of direct competition for specific resources (*see* Baddeley, 1986 and Baddeley *et al.*, 1986 for details).

The performance of a group of mild-to-moderate AD patients was compared with a group of elderly normal controls matched for age, and with a group of young subjects. The AD patients were substantially more impaired by the combined tasks than were the normal elderly, who showed no greater tendency for performance to be disrupted under equated dual task conditions than did the young. Baddeley *et al.* (1986) interpreted their results as supporting the central executive deficit hypothesis. The fact that the young and the normal elderly showed comparable patterns of performance under dual task conditions suggests that adapting the level of difficulty of the constituent tasks is an appropriate control for the effects of general processing load, since the normal elderly did show an impairment in performance of the constituent tasks when they and the young were tested under equivalent conditions.

While the results are consistent with the central executive hypothesis, at least 2 of the 3 conditions are open to an alternative explanation. First of all, the effects of articulatory suppression were very slight, and did not produce a significant interaction with patient condition (single vs dual task). The effect of concurrent reaction time was much clearer, with the predicted interaction occurring in both the effect of reaction time on tracking and on the effect of tracking on reaction time. However, it could be argued that the reaction time task was considerably more difficult for the AD patients, and that the overall information processing load of tracking combined with reaction time was thus substantially greater for these subjects. The case rests therefore only on the third condition in which cognitive and digit span were combined, with the overall level of performance adjusted so as to make the 2 constituent tasks equally difficult for all 3 groups. Here there was a highly significant interaction between groups and single vs dual task performance, whether this was measured in terms of tracking or in terms of memory span, thus supporting the hypothesis of a central executive deficit.

The present study aims to explore the central executive hypothesis in more detail. Two experiments will be presented. Experiment 1 involved retesting the AD patients studied by Baddeley *et al.* (1986) and their age-matched controls over time. If the central executive deficit is as crucial as suggested, then the requirement to combine 2 tasks should produce an ever-greater deficit as the illness progresses. Such a longitudinal design has the advantage of using each subject as his or her own control, hence avoiding some of the problems of comparability between patients and controls observed in earlier studies. One of the experiments that follow therefore studies the capacity of AD patients to combine tracking with articulatory suppression, simple auditory reaction time and digit span when tested on 3 occasions separated by intervals of 6 mths.

An alternative interpretation, however, might be that anything that makes a task more difficult will differentially penalize AD patients. This can be contrasted with the central executive deficit hypothesis which predicts that certain types of difficulty will be particularly sensitive to the effects of AD. More specifically, it suggests that coordination of 2 concurrent tasks will be one important role of the central executive, and hence that dual task performance should be more sensitive than a simple within-task increase in difficulty.

Experiment 2 therefore addresses the difficulty hypothesis, by studying the effect of difficulty level on a categorization task, both in a cross-sectional and in a longitudinal design. It is well established that categorization becomes increasingly difficult as the number of categories from which a target is selected increases, where difficulty is measured by error rate and reaction time (e.g. Murdock, 1965; Baddeley *et al.*, 1984). If the greater impairment for AD patients with dual tasks (Baddeley *et al.*, 1986) is explained in terms of the general difficulty of the task, we would expect AD performance on the most difficult version of the categorization task to deteriorate over time, much more so than for the easier version of the task.

EXPERIMENT 1: LONGITUDINAL TRACKING

Subjects

AD patients. The initial test (Baddeley *et al.*, 1986) involved a total of 28 AD patients who formed part of a larger sample, described by Della Sala *et al.* (1986), of patients referred to the neurological service in Milan over a 3-yr period. A total of 224 demented people were referred, of whom 129 were provisionally diagnosed as AD patients on the basis of clinical history, neurological examination, CT scan and laboratory data which were used to exclude other possible dementing illnesses. The formal diagnostic criteria have been set out elsewhere (Baddeley *et al.*, 1986; Della Sala *et al.*, 1986), and are broadly in line with those of NINCDS-ARDA (McKhann *et al.*, 1984) and DSM III-R (American Psychiatric Association, 1987). Of these 129, patients were excluded from the present study if they had a presumptive length of illness longer than 4 yrs (i.e. likely to have a 'severe' disease); if there was a history of alcohol abuse; if there was a history of drug abuse with drugs which possibly affect central nervous system functions; if their score was less than 50% in a temporal orientation task (Benton *et al.*, 1964) or less than 70% on the test devised by Della Sala *et al.* (1984) on information about family members; and if their score on a scale of everyday coping ability, a revised version of the NUDS (Canter *et al.*, 1961), was less than 70%. They were also excluded if they were not currently living in a family setting and needed special care or if they did not live within Milan or its hinterland. Other criteria for inclusion were availability and willingness to be tested (and retested), and the capacity to read and write as measured informally.

When all these selection criteria were applied, the initial sample of 129 referrals reduced to a sample of 28 patients (22%), comprising 12 men and 16 women. These 28 patients all showed a clinical pattern of dementia associated with AD, together with evidence of deterioration over the previous 6-mth period. This sample constituted the 28 patients who took part in the initial study by Baddeley *et al.* (1986). They were subsequently followed up and tested on 2 further occasions, each separated by a gap of about 6 mths. By the third test, the number of patients still participating in the study had dropped to 15, the other 13 subjects having either died or deteriorated to a point at which they were no longer capable of following experimental instructions. Table 1 shows the characteristics of the experimental samples in the 3 testing sessions. Data refer to the first testing session.

The subgroups of 'survivors' did not appear to differ demographically from the other patients, nor did they differ in level of performance on any of the wide range of psychometric and neuropsychological measures taken on these subjects (*see below*).

TABLE 1. FEATURES OF THE EXPERIMENTAL SUBJECTS ENTERING THE STUDY

	Testing sessions					
	I		*II*		*III*	
	AD/pts (n = 28)	*Controls (n = 28)*	*AD/pts (n = 20)*	*Controls (n = 18)*	*AD/pts (n = 15)*	*Controls –*
(i) Tested subjects						
Age (yrs)	64.9 (7.0)	64.0	64.2 (7.6)	64.4 (5 1)	64 2 (7.0)	–
Ed level (yrs)	9.5 (4.3)	9.2 (3.7)	9.3 (4.6)	9.4 (3.0)	9.8 (4.9)	–
Age at onset (yrs)	63.0 (7.2)	–	62.6 (7 7)	–	62.7 (8.0)	–
Male/female ratio	0.75	0.86	0.54	0.80	0 66	–
Length of illness (mths)	21.2 (14.1)	–	18 9 (14.8)	–	17.6 (16.4)	–
Raven's PM (range 0–48)	18 0 (11.1)	–	17.8 (10.7)	–	19.5 (10.6)	–
Token Test (range 0 36)	24.8 (7.8)	–	25.0 (7.5)	–	26.7 (5.9)	–
Street CT (range 0 14)	4.8 (3.2)	–	4.6 (3 2)	–	4.8 (3.3)	–
			AD/pts (n = 8)	*Controls (n = 10)*	*AD/pts (n = 5)*	*Controls –*
(ii) Drop outs						
Age (yrs)			66.8 (5.7)	64.2 (4.7)	54.2 (8 1)	–
Ed. level (yrs)			10.1 (3.9)	9 3 (3.9)	7.8 (3.3)	–
Age at onset			63.6 (6.3)	–	62.6 (7 5)	–
Male/female ratio			3 0	0 50	0.25	–
Length of illness (mths)			17.0 (10.6)	–	22.8 (8.9)	–
Raven's PM (range 0.48)			20.5 (8.9)	–	12.5 (10.8)	–
Token Test (range 0.36)			25.2 (9.2)	–	18.5 (9.9)	–
Street CT (range 0.14)			4.2 (3.3)	–	4.0 (3 4)	–

Standard deviations are given in parentheses.

Of the 28 initial AD patients 8 dropped out of the study before the second test (*see* Table 1). Two died as a result of stroke or cardiac disease, 1 had developed laryngeal cancer, 1 refused to be retested and 4 were unable to perform the tests because of a general cognitive deficit. One of these was sufficiently severe as to be institutionalized, 1 showed a severe spatial exploration deficit similar to Balint-Holmes' optic ataxia and 2 showed perseverative behaviour, mirroring that found in a frontal syndrome. Between the second test at 6 mths (mean interval 6.8 mths, SD = 1.7), and the third at 1 yr (mean interval 13.9 mths, SD = 1.9), a further 5 patients dropped out. Three of these showed a severe optic ataxia that rendered the tracking task impossible, 1 showed inertia, presumably due to a frontal syndrome that was sufficiently marked to make testing impossible, while a fifth refused to be tested.

Of the 15 remaining patients who made up the longitudinal group, 3 showed a CT scan that was normal given their age, 5 showed gross atrophy, while 7 had minimal-to-moderate atrophy. On a standard neurological examination, 6 patients showed 'release signs' (chiefly glabellar blink and snout reflex) or paratonia. Some degree of motor impersistence was also found in 5 patients, but apart from 1 patient presenting with some degree of extrapyramidal rigidity, there were no other physical signs of neurological impairment.

Performance of the control group was measured on a short psychometric battery which is also shown in Table 1. These tests were included in order to have the opportunity to check, on a wider range of cognitive performance, whether the AD patients dropping out along the longitudinal assessments did so because of a strictly cognitive difference. The tests were Raven's Progressive Matrices (1938) sets A, B, C and D (score range 0–48) as a measure of non-verbal intelligence, the Token Test (De Renzi and Faglioni, 1978) as a test of language comprehension (score range 0–36) and the Street Completion Test (Street, 1931) as a measure of visuo-perceptual ability (score range 0–14). Normative data for these tests have been collected on a sample of 321 normal subjects in a separate study (Spinnler and Tognoni, 1987). These normative data set the median value for these tests at the following scores: Raven's 28.5, Token 33 and Street 7. The inferential score above which fall the scores for 95% of the population are Raven's 15, Token Test 26.5 and Street Test 2.25. Table 1 shows the mean performance for each of these tests for the patients that took part in all three testing sessions. The data shown were all collected on the first testing session. These scores are indicative of intellectual impairment, with 7 of the 15 longitudinal patients scoring at below the fifth percentile level on Raven's Matrices, 9 scoring below this cut-off for the Token Test, and 4 below the fifth percentile of the Street Test. Performance in this psychometric battery suggests that the surviving AD patients were affected by a relatively mild and slow progressive form of the disease. While they showed few differences from the non-surviving patients on the initial test, it would be unwise to assume that they are a typical sample of all AD patients.

Elderly group subjects. While the principal point of interest involved longitudinal changes in performance of the AD patients, it was considered wise to include a group of normal elderly to serve as a baseline control, to ensure that any decrements that were found were truly characteristic of AD patients, and not attributable to inherent variability in test performance. The control subjects comprised normal subjects matched on age and educational background with the AD patients, but free of evidence of present or past nervous, organic or physical disease that might be expected to impair cognitive performance. They comprised 8 men and 10 women and were tested on 2 occasions separated by a delay of 6 mths (mean interval 6.6 mths, SD = 1.4). They were not retested a third time. Demographic characteristics are given in Table 1.

Experimental procedure

Tracking. The primary task presented to all subjects required them to keep a light-sensitive stylus (light pen) placed on a white square (2×2 cm) moving randomly about the screen of a colour computer monitor. The square remained white as long as the light pen was in contact, but changed to orange immediately contact was lost, returning to white when contact was regained. In the initial *adaptive* phase, the square initially moved quite slowly, with the speed gradually increasing until a point was reached at which the subject failed to maintain contact for more than 60% of the time. At each speed, performance was summed over a period of 20 s before being increased.

The process was controlled by an Apple II computer and took about 4 min to identify the point at which performance approximated 60% time-on-target.

The subject was then given 3 20 s periods of tracking at the 60% time-on-target level. If the subject improved to beyond 60%, then the difficulty level was adjusted and 3 further 20 s trials were given. This procedure continued until the subject's performance had stabilized at some point between 40% and 60%

time-on-target. This completed the *adaptive* tracking phase, and the final level of difficulty was then used for the remainder of that session. The same level of difficulty was used on the retests 6 and 12 mths later, without any readaptation. This was done to allow us to assesss any decrement in performance over time as measured by time-on-target. Subsequent runs in each test session involved combining tracking with other tasks. Since the task was potentially tiring, test runs were limited to 2 min, with the monitor screen at an angle of 30 degrees from the horizontal, since this was found to be less physically tiring than attempting to track on a vertical screen. The standard tracking task was then combined with 3 concomitant tasks in an order that was counterbalanced across tasks, and that was equivalent for AD patients and control subjects.

Concomitant tasks

Articulatory suppression. Subjects were required to count from 1 to 5 repeatedly at a regular rate of approximately 2 per s. This rate was demonstrated by the experimenter who monitored the subject's performance, encouraging speeding up if articulation rate dropped.

Reaction time to tones. Subjects were presented with a sequence of clearly audible tones from a loudspeaker, and required to press a footswitch as rapidly as possible in response to each tone. Inter-tone interval varied randomly between 4 s and 6 s, producing between 23 and 25 tones within each 2 min test run. On each session, the tones began a few seconds before the start of the 2 min run so as to ensure that the subject was performing the reaction-time task. Reaction time and any missed signals were recorded by an Apple II computer.

Memory span. Memory span was first established using the standard auditory digit-span technique in which subjects were read out a list of digits at a rate of 1 per s and asked to repeat them back in the same order. Testing began with a single digit, and was incremented by 1 digit until a point was reached at which the span was exceeded. Subjects were presented with 3 sequences at each length, and testing ceased when the subject was unable to recall 2 of the 3 sequences. For the purpose of the present study, the subject's span was assumed to be 1 digit less than this. Hence if a subject had been successful on all occasions at length 6 but had failed 2 of the 3 at length 7, he would subsequently be presented with sequences of 6 digits. Subjects were then tested for a 2 min period during which they performed the span test alone, and for a further 2 min during which they combined digit span with tracking. In each case, performance was measured in terms of the percentage of sequences that were recalled completely correctly. The number of lists presented during the 2 min test depended of course on the length of the individual subject's span, and ranged from 11 to 15 sequences. As with tracking, the digit memory task can be adjusted to a level of difficulty appropriate for the ability of each individual subject. The span was reassessed on each of the 3 test sessions. By recording the number of errors produced by subjects, we have a means to equate initial group performance.

To summarize, subjects were required to perform the tracking task alone, followed by the 3 dual task conditions in counterbalanced order. The subjects who remained testable on the subsequent test sessions were tested in the same counterbalanced order, as were the age-matched controls.

Results

Demographic and psychometric data from the AD patients were subjected to a series of one-way ANOVAs to determine whether any of the subject variables measured on the first test session could distinguish between patients who could be retested and those who could not, either on the second or third testing session. The 4 patients who could not be retested for reasons unrelated to severity were not included in these analyses. The variables tested were age, years of formal education, length of illness, performance on the Raven's Matrices, performance on the Token Test and performance on the Street Test. The analyses revealed that none of these measures significantly discriminated between these subgroups of patients.

We carried out a similar series of analyses on our single and dual task performance measures. Once the level of significance had been adjusted for multiple comparisons, only one of the measures significantly discriminated between the groups, namely response time to tones when these were combined with tracking [$F(1, 20) = 11.17$; $P < 0.005$]. The mean RT for the group tested on all 3 occasions was 828 ms, and for the 'drop-outs' was 1298 ms.

Next, we considered the performance measures from the 3 different testing sessions. The principal prediction of the central executive deficit hypothesis is that as dementia progresses, its effect on dual task performance should be disproportionately greater than its effect on performance of the constituent task. Therefore the main analyses considered the extent to which the difference between single and dual task performance interacted with test session. It is possible that performance on any task will deteriorate over time with AD patients. In order to investigate this possibility, we also analysed data over 3 test sessions for the response to tones task when performed alone. Finally, we carried out subsidiary analyses on the 20 AD patients who performed on test sessions 1 and 2. In all cases, the mean data for this group were very similar to those for the subgroup who completed all 3 test sessions. Therefore only the data for this latter subgroup are reported.

Tracking and articulatory suppression. Table 2 shows the mean performance of the AD patients and the normal controls over successive tests. In order to illustrate changes in dual task performance over time, Fig. 1 shows the dual task tracking performance expressed as a percentage of single task performance.

TABLE 2 MEAN TRACKING PERFORMANCE, AS MEASURED BY PERCENTAGE TIME ON TARGET, AS A FUNCTION OF PATIENT GROUP, EXPERIMENTAL CONDITION AND TEST SESSION

	Test session		
	I	*II*	*III*
AD patients			
Tracking alone	59.8	61.8	65.5
+ suppression	54.0	48.3	47.8
+ tones	51.7	46.9	37.7
+ digit span	42.2	34.9	30.1
Normal elderly			
Tracking alone	54.3	54.9	–
+ suppression	52.4	53.3	–
+ tones	53.3	51.5	–
+ digit span	48.4	46.6	–

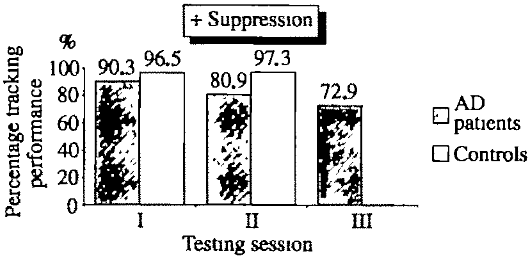

FIG. 1. Tracking performance with concurrent articulatory suppression as a percentage of single task performance for Alzheimer patients and normal elderly subjects

In the case of the AD patients who completed all 3 test sessions, analysis of variance indicated a significant main effect of suppression [F(1, 14) = 39.5, $P < 0.001$] together with the predicted interaction between the presence of suppression and test session, with suppression having an ever-increasing effect on performance as the disease progresses [F(2, 28) = 4.4, $P < 0.025$]. When we considered the data for the larger groups of patients who completed only test sessions 1 and 2, there was again a significant disruption by suppression [F(1, 19) = 18.45, $P < 0.001$], but there was no effect of test session and no interaction. With the normal elderly there was no significant effect of suppression on tracking [F(1, 17) < 1], and no effect of test session [F(1, 17) < 1].

Tracking and response to tones. Fig. 2 shows the effect of reacting to auditory tones on tracking performance as a function of test session, expressed as a percentage of single task performance. The mean performance of AD patients and elderly controls over successive tests are shown in Table 2. Over 3 test sessions, once again the AD patients show both a clear effect of tones on tracking [F(1, 14) = 81.64, $P < 0.001$], and an interaction of this effect with test session [F(2, 28) = 18.57, $P < 0.001$].

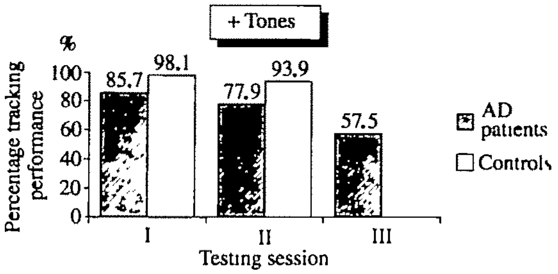

FIG 2 Tracking performance with concurrent reaction to tones as a percentage of single task performance for Alzheimer patients and normal elderly.

Over 2 test sessions, the ANOVA revealed a significant effect on tracking of responding to tones [$F(1, 19) = 34.76, P < 0.001$], an effect that interacted with test session [$F(1, 19) = 5.18$; $P < 0.05$]. There was not a significant effect of test session overall. In the case of the normal elderly, there was no significant effect of tones on tracking, and no interaction with test session, and no effect of test session overall [$F(1, 17) = 1.915$, 1.106 and 0.061, respectively].

Table 3 shows the mean reaction times to auditory tones with and without tracking. Unfortunately, the timing data for 1 AD patient was not recorded, reducing the number to 14 for this analysis. There was a main effect of concurrent tracking on reaction time [$F(1, 13) = 28.77$, $P < 0.001$], an effect of test session [$F(2, 26) = 7.63$, $P < 0.01$] and an interaction between the tracking effect and session [$F(2, 26) = 5.51, P < 0.01$]. The ANOVA on single task performance revealed that there was no tendency for response time to change over time ($F < 1$). This confirms that the change over time was due solely to performance on the dual task condition.

TABLE 3. MEAN RESPONSE TIME (MILLISECONDS) AND MEAN NUMBER OF TONES MISSED AS A FUNCTION OF PATIENT GROUP, EXPERIMENTAL CONDITION AND TEST SESSION

	Test session		
	I	*II*	*III*
AD patients			
Response time alone	767	704	746
+ tracking	828	1011	1184
Missed tones alone	1.7	3.9	4.5
+ tracking	7.7	13.0	16.1
Normal elderly			
Response time alone	398	418	–
+ tracking	461	503	–
Missed tones alone	0.0	0.2	–
+ tracking	0.2	0.3	–

Turning back to a comparison of single and dual task performance, there was no overall difference in response time between sessions 1 and 2 ($F < 1$). However, there was a highly significant effect on reaction time of concurrent tracking with the 18 subjects for whom these data were recorded [$F(1, 17) = 16.96$; $P < 0.001$], an effect that interacted with test session [$F(1, 17) = 4.44$; $P < 0.05$].

In the case of the normal elderly, there was a significant effect of tracking on reaction time [$F(1, 17) = 34.56, P < 0.001$], but no effect of test session [$F(1, 17) = 2.99$] and no interaction between the effect of tracking and test session [$F(1, 17) = 1.82$].

Table 3 also shows the mean number of errors of omission in which subjects failed to respond to a tone. In the case of the AD patients, concurrent tracking significantly increased the probability of missing a signal [$F(1, 14) = 57.09$, $P < 0.01$]. Missed signals increased as a function of test session

[F(2, 28) = 11.96, $P < 0.001$], an effect that interacted with tracking [F(2, 28) = 3.88, $P < 0.05$]. An analysis of single task performance indicated that the number of missed tones did not alter over time [F(2, 28) = 2.64].

Over 2 test sessions, the number of missed tones increased [F(1, 19) = 16.39; $P < 0.001$], and also increased when the response task was combined with tracking [F(1, 19) = 41.20; $P < 0.001$]. However, these variables did not interact [F(1, 19) = 2.06].

The normal elderly subjects showed a significant effect of concurrent tracking on the tendency to miss signals [F(1, 17) = 4.50, $P < 0.05$], but this effect did not increase over sessions [F(1, 17) = 1.51], nor was there an interaction between the effect of tracking and session ($F < 1$).

Tracking and concurrent digit span. Table 2 shows the mean tracking with and without concurrent digit span for AD patients and the elderly controls. Fig. 3 shows dual task performance on tracking as a percentage of single task tracking performance. In the case of the AD patients, concurrent span significantly impaired tracking [F(1, 14) = 110.5, $P < 0.001$]. There was not a significant effect of test session on performance ($F < 1$), but there was a significant interaction between the effect of concurrent load and test session [F(2, 28) = 8.05, $P < 0.01$].

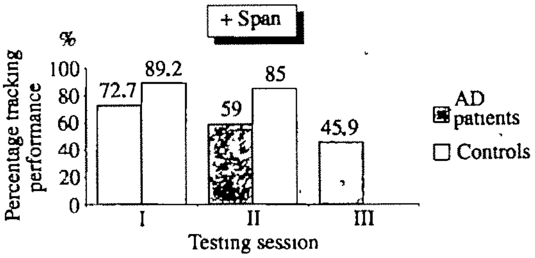

FIG. 3. Tracking performance with concurrent digit span as a percentage of single task performance for Alzheimer patients and normal elderly subjects.

For the 20 AD patients who completed just 2 test sessions, there was a significant drop in tracking performance when combined with span [F(1, 19) = 81.49; $P < 0.001$], an effect that interacted with test session [F(1, 19) = 8.48; $P < 0.01$], but there was no effect of test session overall ($F < 1$).

In the case of the normal elderly, concurrent span had a significant effect on tracking [F(1, 17) = 14.19, $P < 0.01$], but there was no effect of test session ($F < 1$), and no interaction between the concurrent digit effect and test session [F(1, 17) = 1.71].

Table 4 shows the effect of tracking on digit span errors. In the case of the AD patients, there was a main effect of tracking on errors [F(1, 14) = 285.96, $P < 0.001$], a main effect of test session [F(2, 28) = 12.44, $P < 0.001$] and a significant interaction between the tracking effect and test session [F(2, 28) = 8.22, $P < 0.01$]. Over 2 test sessions, there was an effect on span performance when this was combined with tracking [F(1, 19) = 158.53; $P < 0.001$]. In addition, span performance was poorer on the second test session [F(1, 19) = 6.41; $P < 0.05$], but this did not interact with the effect of concurrent tracking [F(1, 19) = 2.71].

Digit span was assessed on each of the 3 test sessions. Mean memory span, indicating the point at which performance ceased to be perfect, did not decline significantly, being 4.2, 4.3 and 4.1 for sessions 1, 2 and 3, respectively [F(2, 28) = 1.77]. However, there was a small but significant increase over time in the number of errors made subsequently when subjects were performing the span task alone, as shown in Table 4 [F(2, 28) = 3.76; $P < 0.05$].

The normal elderly showed a significant effect of concurrent span on tracking [F(1, 17) = 38.52, $P < 0.001$], but no effect of test session ($F < 1$) and no interaction between the tracking effect and test session ($F < 1$).

Discussion

Our results indicate that articulatory suppression, concurrent reaction time and concurrent digit span all disrupt tracking in AD patients, and that the extent of this disruption increases systematically over 3 successive tests, separated by 6-mth intervals. The influence of such secondary tasks on tracking in the

TABLE 4. MEAN ERRORS IN DIGIT SPAN PERFORMANCE AS A FUNCTION OF PATIENT GROUP, EXPERIMENTAL CONDITION AND TEST SESSION

	Test session		
	I	*II*	*III*
AD patients			
Errors in span alone	1.5	5.3	6.3
+ tracking	39.1	48.4	62.8
Normal elderly			
Errors in span alone	3.8	4.1	–
+ tracking	22.3	22.6	–

normal elderly group was consistently less, and showed no evidence of increasing over successive tests. As such, the results are consistent with the hypothesis that AD patients characteristically suffer from an impairment in their ability to coordinate performance on 2 tasks, and this is consistent with these patients having a deficit of the central executive component of working memory.

The tracking task was chosen to involve the operation of the visuo-spatial scratchpad. The 3 concurrent tasks were chosen so as to have little or no direct loading on this component of working memory, and hence as tasks which will interfere with tracking only in as far as they and tracking make demands on the central executive.

In the case of articulatory suppression it may be recalled that it was not sufficient to produce any significant impairment in the earlier study (Baddeley *et al.*, 1986), nor does it have any impact on tracking in the normal elderly tested in the present study. This is consistent with the fact that repeatedly counting from 1 to 5 is a relatively undemanding overlearned task that loads principally the phonological loop system. Also, it has little influence on the operation of the visuo-spatial scratchpad which is heavily involved in tracking performance (Baddeley and Lieberman, 1980). As dementia progresses, however, even the undemanding task of articulatory suppression is sufficient to interfere progressively more with concurrent tracking. It seems implausible to assume that articulatory suppression involves an increase in spatial processing over time, and hence the obvious interpretation is that even the relatively minor load of coordinating tracking with an overlearned counting task is sufficient to cause substantial impairment in performance. These results are in line with those of Morris (1984, 1986) who observed that the operation of the phonological loop was not qualitatively impaired in AD patients. However, articulatory suppression was sufficient to cause the forgetting of verbal material over a brief delay in AD patients, while normal elderly subjects were quite capable of maintaining items in memory with no apparent disruption from suppression. Morris (1986) interpreted this result as reflecting an impairment in patients' dual task performance rather than a deficit in the phonological loop *per se*.

It is perhaps less surprising that AD patients show interference between tracking and concurrent simple reaction time, since it is plausible to assume that both of these draw upon some central processing capacity. The clear and systematic decrement in the capacity to timeshare these 2 tasks is, however, striking, showing up as it does on the tracking task, and on both reaction time and errors of omission. This same deterioration over time does not appear reliably for single task performance, although it is important to bear in mind that the patients who have deteriorated the most are probably the ones who will not have been retested Therefore, our findings are necessarily a conservative estimate of the degree of performance decrement over time for AD patients in general. Nevertheless, the crucial feature of these results is not the fact that tracking and reaction time decline, but rather that the capacity to combine the two appears to be particularly sensitive to the progressive cognitive deterioration that accompanies Alzheimer's disease.

One might argue that articulatory suppression and the concurrent reaction time measure become progressively harder as the patient deteriorates. For that reason, the third condition is crucial, since digit span was adjusted so as to ensure that subjects were performing at an equivalent level on each of the 3 sessions. Once again, the decrement in dual task performance was consistent and progressive, suggesting that the capacity to combine 2 tasks is more sensitive to the progressive deterioration than is performance on either of the 2 constituent measures.

Alzheimer's disease gives rise to a wide range of cognitive deficits, any one of which might potentially be used diagnostically or prognostically. We initially hoped that the analysis of drop-out from our 2 studies would allow an assessment of prognostic value of the various cognitive measures used. In fact only 1 was associated significantly with drop-out, namely time to react to tones while tracking. While the association was quite strong [F(1, 20) = 11.17, $P < 0.005$] the fact that other measures of central executive functioning are not predictive suggests we should not draw strong theoretical conclusions from this one result. It may well be the case that drop-out from the study is simply too multi-faceted to be predicted by a purely cognitive measure. In some cases, patients died from further diseases, while in others a single symptom such as optic ataxia was sufficient to render the patient unable to perform the tracking task, regardless of the general level of cognitive functioning.

An alternative approach to assessing the diagnostic value of the performance measures might have been to explore the association between degree of cortical atrophy (as measured by CT scans) and degree of cognitive performance impairment in our patient sample. However, previous attempts to do so have reported findings that are at best contradictory, and a number of authors have failed to show a clear relationship (Kopelman, 1989; for a review *see* Naugle and Bigler, 1989). The correlations between atrophy and neuro-psychological deficits increases with the severity of the disease (de Leon and George, 1983; Eslinger *et al.*, 1984), and our sample was in a very mild stage of deterioration. Furthermore, since this was a longitudinal study, a comparison between cortical atrophy and performance measures would have required CT scans of each of the 3 testing sessions. In our case, the CT scans were obtained purely for diagnostic purposes prior to the first testing session. For these reasons, we felt that it was inappropriate to attempt to study the relationship between atrophy and cognitive impairment.

The central executive deficit hypothesis is not the only plausible interpretation of our data, and one could argue that the demented subjects were more sensitive to dual tasks simply because they are more difficult than single tasks. In order to investigate this possibility, we carried out a second experiment with our samples of patients and normal elderly. This involved the categorization task in which the subject was shown a target category such as *animals*, together with a possible example such as a *cat*, or a *chair*, and must press a 'yes' key if the target word is a member of the category, while making no response if it is not. Difficulty was manipulated as a within-task factor by simultaneously presenting 1, 2 or 4 different category names in association with each individual target word. Increasing number of alternative categories is known to increase difficulty as measured by response latency (Yntema, 1963). This increase is probably principally due to slowing of semantic memory access, a process that does not appear to be heavily dependent on working memory capacity (Baddeley *et al.*, 1984). Such a task thus provides a good potential test of the difficulty hypothesis; any increase in difficulty should differentially affect AD patients, with patients showing an effect of number of alternatives on response latency that should become more marked as the disease progresses. On the other hand, if dual task coordination is the crucial deficit, there is no reason to expect within-task difficulty to show the marked interaction with test session shown in Experiment 1.

As with the tracking task (*see also* Baddeley *et al.*, 1986), we investigated performance on the categorization task on a first test session, comparing the results of AD patients and those of a group of normal elderly. Then performance of AD patients was tested approximately 7 mths later. In order to check the stability of the categorization test over time, as for Experiment 1, the elderly also were tested on 2 occasions.

EXPERIMENT 2: CATEGORIZATION TASK

Cross-sectional study

Subjects

AD patients. This experiment was started 8 mths after the first test session for Experiment 1. During this interval, 42 patients were added to the main sample of 129 AD patients, following the same diagnostic procedure as before. The timings of Experiments 1 and 2 were such that only some of the patients in Experiment 1 could take part in Experiment 2. Of the 28 patients who took part in Experiment 1, 17 also took part in Experiment 2. Of the extra 42 patients mentioned above, 13 were suitable for inclusion in Experiment 2, giving a total of 30 subjects in this experiment (13 male and 17 female).

Their mean age was 65.1 yrs (SD = 5.2), and the range was 51−80 yrs. They had a mean of 9.4 yrs of formal education (SD = 4.1, range 5–17 yrs). The mean period between diagnosis of illness onset and testing was 2 yrs (SD = 1.7), with a range of 1–4 yrs.

Of the 30 patients entering the study, CT scans of 5 patients showed a degree of atrophy which could be fully explained by their age, 9 had grossly evident atrophy, and 16 had a mild to moderate atrophy. At the time of testing, 2 of them showed an atrophy more marked in the left perisylvian region. Their overall neurological examination was normal, with the exception of 16 patients showing some of the so-called 'release signs', or paratonia, and 3 presenting some degree of extrapyramidal rigidity.

In order to give an indication of the general degree of cognitive impairment, we report here the scores obtained on the small set of psychometric tests used for Experiment 1. Mean score on the Raven's Progressive Matrices was 15.4 (SD = 10.4), mean score on the Token test was 24.7 (SD = 8.5), and mean score on the Street test was 4.8 (SD = 3.1).

Control group. We also tested a group of 30 normal elderly subjects, 14 males and 16 females. Their mean age was 64 yrs (SD = 4.1, range 57–76), and their mean educational level was 9.5 yrs (SD = 3.2, range 5–17). These were comparable with the characteristics of the demented group.

Experimental procedure

The basic task involved is that of presenting subjects with a target category and names of items which may (correct 'yes' answer) or may not (correct 'no' answer) belong to the target category. The subject's task was to press a key with his or her preferred hand, only when the item presented belonged to the target category. This response gave rise to a correct 'yes' answer. The name of the target category was displayed in the centre of a computer screen, and the name of each item was displayed at the bottom of the screen. The test comprised 3 conditions: in condition 1, only 1 target category was present, and the items were drawn from 2 categories, 1 of which was the target category; condition 2 was a more complex version of the same task, where the number of target categories was increased to 2, drawn from a total of 4 possible categories. These 2 categories were displayed side by side in the centre of the computer screen; in condition 3, 4 target categories were displayed in a row in the centre of the screen, the categories being drawn from a total pool of 8. Testing was always in the same order, systematically increasing the number of target categories.

On each testing session, the target categories were chosen at random, from a group of 8, and the items were chosen at random from a set of 16 exemplars of each category. The categories used were animals, jobs or professions, colours, articles of clothing, cities, fruits, means of transport and male names. Category exemplars were chosen to be high frequency items from each of these categories (Battig and Montague, 1969), with the exception of cities and male names, where common Italian cities and names were chosen. Target categories remained on the screen while the items were presented for a maximum of 4 s, unless terminated by a response. The presentation of each item was accompanied by an auditory warning signal. Total testing time for all 3 conditions was between 8 and 9 min. The response time was measured from the onset of each item until a keypress was recorded, or the 4 s display time was complete. Subject performance was measured both in terms of accuracy and mean response time. The maximum accuracy score possible was 32, with a score of 16 indicating chance performance. The presentation of the stimuli and the timing and recording of keypresses were controlled by an Apple II plus computer.

Results

First we analysed the number of correct responses for the elderly controls and the AD patients, for 1, 2 and 4 categories. Mean scores are shown in Table 5. Analysis of variance revealed a significant effect of group. [$F(1, 58) = 62.15, P < 0.001$]; a significant effect of number of categories: [$F(2, 116) = 18.11, P < 0.001$]; and a significant group by category interaction: [$F(2, 116) = 9.56, P < 0.001$]. It is clear from the table that the controls show little if any drop in accuracy with increasing number of categories, and their performance is essentially at ceiling. This is supported by non-significant *post-hoc* pairwise comparisons between the means (Studentised Range Statistic, Q). In contrast, the Alzheimer group show a substantial drop in accuracy with increasing number of categories from 1 to 2 categories ($Q = 8.05$, $P < 0.01$), or 1 to 4 categories ($Q = 9.61, P < 0.01$). Increasing from 2 to 4 categories made no difference to the number correct. All the means for the Alzheimer group were significantly poorer than all of the means for the elderly controls ($P < 0.01$ in all cases).

We also analysed the incorrect responses, separating them according to whether they were misses or false alarms. Data are shown in Table 5.

TABLE 5. ACCURACY AND SPEED OF SEMANTIC CATEGORIZATION AS A FUNCTION OF PATIENT GROUP AND NUMBER OF CATEGORIES

	Number of categories		
	1	*2*	*4*
AD patients			
Correct (max. = 32)	27.2	23.8	23.1
Misses	2.6	4.6	5.5
False alarms	2.2	3.6	3.4
Correct RT	1588	2030	2335
Normal elderly			
Correct (max. = 32)	31.6	31.3	30.7
Misses	0.1	0.0	0.6
False alarms	0.4	0.7	0.6
Correct RT	620	741	918

For the misses, there was a main effect of group: [F(1, 58) = 48.94, $P < 0.001$], and an effect of category number: [F(2, 116) = 12.51, $P < 0.001$], and these variables interacted: [F(2, 116) = 6.98, $P < 0.001$]. *Post-hoc* comparisons supported the group difference ($P < 0.01$), and the interaction. The means for the control group did not differ. The mean for 1 category in the Alzheimer group differed from that for 2 categories ($P < 0.01$) and for 4 categories ($P < 0.01$). The difference between 2 and 4 categories was not significant.

For the false alarms, there was a significant difference between the groups: [F(1, 58) = 13.24, $P < 0.001$]; and a significant increase with category number: [F(2, 116) = 5.21, $P < 0.01$]. These variables did not interact: [F(2, 116) = 2.17]. *Post-hoc* comparisons supported the difference between the groups in that all the means for the AD patients were poorer than those for the normal elderly ($P < 0.01$).

Next, we conducted the same analysis for the correct response times. The mean data are shown in Table 5. There was a main effect of group: [F(1, 58) = 126.78, $P < 0.001$]; a main effect of number of categories: [F(2, 116) = 64.29, $P < 0.001$]; and a significant interaction: [F(2, 116) = 12.56, $P < 0.001$]. Here, for the control group, there appeared to be an increase in response time with increasing number of categories (1 vs 4 categories, $Q = 6.45$, $P < 0.01$). However, the *post-hoc* comparison for 1 vs 2 categories was not significant. The Alzheimer group produced much slower responses overall, with all the means significantly slower ($P < 0.01$) than those for the controls. The Alzheimer patients were much more severely affected by increasing the number of categories as evidenced by the significant groups by category interaction. Also, all of the means for each category number were significantly different from one another: 1 vs 2 categories ($Q = 9.58$; $P < 0.01$), 1 vs 4 categories ($Q = 16.19$; $P < 0.01$), and 2 vs 4 categories ($Q = 6.61$; $P < 0.01$).

Longitudinal study

Subjects

AD patients. Of the 30 patients included in the cross-sectional study, 15 (6 males and 9 females), were retested formally at a mean interval of 7.4 mths (SD = 1.8). The 'drop-outs' in 2 cases were due to death. In 3 cases, patients became too severely ill to be retested, that is they did not understand the test instructions. In 2 cases the patients became easily distracted, and their scores were considered unreliable. Two patients became aphasic and alexic, and therefore could not read the words correctly, and 3 of them showed frontal signs that rendered the results unreliable because of a tendency to perseverate. Finally, 3 patients were unwilling to be retested.

For the remaining 15 patients, their mean age at the time of the first test sessions was 64.8 yrs (SD = 7.5, range 51–80), their mean educational level was 10.0 yrs (SD = 4.7, range 5–17) and their mean length of illness was 18.7 mths (SD = 14.5, range 3–48).

Control group. To match the 15 patients, 15 normal elderly controls were chosen randomly from the original group of 30, and 14 of these agreed to be retested. The control group mean age was 65.5 yrs, range 57–76, and their mean educational level was 10.5 yrs, range 5–17. The mean interval between testing sessions 1 and 2 was 6.3 mths (SD = 0.9).

Results

As for Experiment 1, data from the AD patients and the normal elderly were subjected to a series of one-way ANOVAs to determine whether any of the subject variables measured on the first test session could distinguish between patients who could be retested and those who could not. As before, the variables tested were age, years of formal education, length of illness, performance on the Raven's Matrices, performance on the Token Test, and performance on the Street Test. The analyses revealed that none of these measures significantly discriminated between groups.

A similar analysis carried out on categorization performance indicated that neither number of correct responses nor mean response time significantly discriminated when retested from 'drop-out' subjects.

The mean number of correct responses for test sessions 1 and 2 for 15 Alzheimers are shown in Table 6 and Fig. 4. These data were entered into a two-way ANOVA, with 2 repeated measures, namely test session and number of categories. This analysis showed that the demented subjects deteriorated over time: [$F(1, 14) = 6.42$, $P < 0.05$], and performance was poorer with a larger number of target categories: [$F(2, 28) = 8.08$, $P < 0.01$]. However, there was no indication of an interaction between these variables ($F < 1$).

TABLE 6. ACCURACY AND SPEED OF CATEGORIZATION AS A FUNCTION OF PATIENT GROUP, NUMBER OF CATEGORIES AND TEST SESSION

	Test session	*Number of categories* *1*	*2*	*4*
AD patients				
Correct (max. = 32)	1	27.9	25.3	24.7
	2	25.5	23.3	21.8
Misses	1	2.3	3.5	4.0
	2	3.3	5.2	6.1
False alarms	1	1.8	3.2	3.3
	2	3.3	3.8	4.1
Correct RT	1	1613	1855	2195
	2	1821	2206	2347
Normal elderly				
Correct (max = 32)	1	31.6	31.3	31.2
	2	31.6	31.4	31.4
Misses	1	0.1	0.0	0.1
	2	0.0	0.1	0.2
False alarms	1	0.4	0.8	0.6
	2	0.4	0.4	0.4
Correct RT	1	607	784	937
	2	620	783	972

The data for number of errors, both the number of missed target items and number of false alarms are shown in Table 6. An analysis of variance on misses revealed that errors increased with a larger number of categories [$F(2, 28) = 6.23$; $P < 0.01$], but there was no effect of test session [$F(1, 14) = 3.4$] and no interaction ($F < 1$). For the false alarms, there was no tendency for these to change according to number of categories [$F(2, 28) = 2.1$], no effect of test session ($F < 1$) and no interaction ($F < 1$).

The mean correct response times also are shown in Table 6. An analysis of these data showed that the

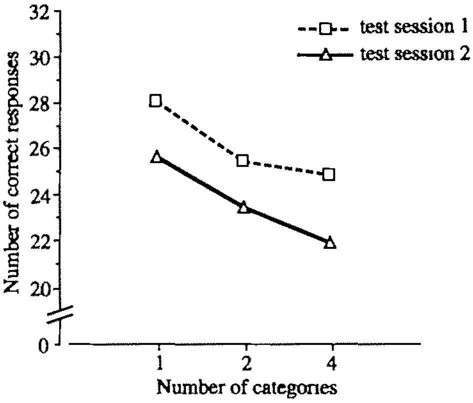

FIG 4. Mean number of correct categorization responses for 15 Alzheimer patients on 2 test sessions.

demented subjects were slower with a larger number of target categories: [F(2, 28) = 26.83, $P < 0.01$]. There was no slowing of responses over time: [F(1, 14) = 2.9], and no interaction (F < 1).

The data for the 14 normal elderly control subjects also are shown in Table 6. For the number of correct responses, it is evident from the table that the control subjects were at ceiling, and therefore formal analyses were considered neither necessary nor appropriate. An analysis of variance on correct response times revealed a significant effect of number of categories [F(2, 26) = 104; $P < 0.001$], but no effect of test session (F < 1), and no interaction (F < 1).

Discussion

The cross-sectional data suggest that increasing the number of categories increases difficulty as measured by response times for both groups, and by accuracy for the AD patients; control subjects made virtually no errors. This pattern is consistent with earlier work (e.g. Yntema, 1963), and suggests that the task is suitable for studying the effect of within-task difficulty on the rate of cognitive deterioration. The clear impairment in performance on this task of the AD group suggests that it is suitable for deciding whether the longitudinal decrement shown in Experiment 1 reflects the vulnerability of the central executive component of working memory, or is simply a reflection of a tendency for rate of performance decrement to increase with task difficulty.

The longitudinal response time data for the group of normal elderly indicated that their performance on this task was stable over time. Both the normal elderly and the demented subjects were affected by the increase in number of categories. In addition, the demented subjects performed more poorly overall on the second test session, as measured by number of correct responses. There was, however, no significant deterioration in response time over test sessions, possibly due to the high variability in this measure for the AD group, although it is also possible that the demented subjects were maintaining their response time at the expense of accuracy.

The data for the demented subjects showed a clear effect on performance of an increase in task difficulty as the number of target categories increased. However, the magnitude of this effect of task difficulty did not increase as the disease progressed. Moreover, there was no indication that this lack of an interaction with time could be due to a floor effect in AD performance. Looking at the data from individual subjects, only 1 of the 15 patients who were retested performed close to chance level, and this occurred only on the second test session. Taken together, these findings support the view that the results for Experiment 1 cannot easily be explained only in terms of task difficulty.

The lack of an interaction of difficulty with time in the dementia patients is a crucial aspect of these data. A possible alternative interpretation of our results from Experiment 1 was that the AD subjects were simply more sensitive to the effects of task difficulty than to the requirement to coordinate dual task performance. This interpretation of our results for AD patients' dual task performance now appears much less convincing.

Any *post-hoc* interpretation in terms of the relative difficulty of different tasks necessarily involves the question as to how difficulty might be measured. A within-task manipulation of task difficulty, such as that used in the categorization task, seems, in part at least, to avoid this risk of circularity. It suggests that the concept of difficulty probably is not sufficient to explain the results of Experiment 1, nor the results of Baddeley *et al.* (1986).

GENERAL DISCUSSION

The results of Experiment 1 showed that demented patients have a particular difficulty with dual task performance, and that this disadvantage becomes more pronounced with the progression of the disease. Notably, performance on the single tasks used in this study did not show this same degree of sensitivity to the deterioration of cognitive ability over time. The findings from Experiment 2 mitigated the possibility that the results from Experiment 1 were due to the overall greater difficulty of dual tasks compared with single tasks, and that the AD patients were simply more sensitive to task difficulty than were the normal elderly. This reinforced the importance of the dual task nature of the tasks used in Experiment 1.

The results of these 2 experiments therefore support the view that AD patients suffer from a deficit in their ability to cope with the cognitive processing necessary for carrying out 2 tasks simultaneously. These results coupled with the conclusions of Baddeley *et al.* (1986), Morris (1986), Becker (1988) and Spinnler *et al.* (1988) are consistent with the hypothesis of a deficit in Alzheimer's disease of the central executive component of working memory.

The central executive is essentially concerned with attentional control. To what extent could other models of attention account for our results? One such model assumes that subjects have a limited pool of attentional resources, with greater task demands using more of this capacity leading to impaired performance when 2 tasks compete (e.g. Kahneman, 1973). While this view was influential in the 1970s, in recent years it has become increasingly clear that it is oversimplified (Wickens, 1984). In particular, it has difficulty in accounting for evidence suggesting separable modular sub-systems. A verbal task such as articulatory suppression can be shown to impair other verbal tasks such as digit span, or verbal reasoning, but has little effect on visuo-spatial tasks such as pursuit tracking or tests of spatial manipulation (Baddeley and Lieberman, 1980; Farmer *et al.*, 1986; Logie *et al.*, 1990). Moreover, when applied to our own data, such an interpretation would presumably predict an interaction with difficulty for both the dual tasks studied in Experiment 1, and the unitary tasks used in Experiment 2; the results of Experiment 2 are not in agreement with this prediction.

One development from the earlier limited resources model has been concerned with the concept of automaticity, the tendency for certain types of skill to reduce their attentional demands as learning proceeds. This allows such skills to be performed with little interference from other concurrent tasks (Schneider and Shiffrin, 1977). It has been argued (Jorm, 1986) that such automatized skills are particularly resistant to the effects of Alzheimer's disease. However, the concept of automaticity is consistent with any attentional model that assumes limited processing capacity, including the working memory model. Furthermore, the concept of automaticity does not bear directly on the interpretation of our present results, which depend on the performance of relatively novel tasks for which there is likely to be little automatization.

One can argue that the dementing process in AD calls for progressively more control resources, even for tasks that in the normal elderly brain continue to run quasi-automatically (Spinnler, 1991). This increasing demand on the central executive functions of time- and accuracy-sharing in AD patients renders them particularly sensitive to tasks and conditions whose 'difficulty' stems from their central executive involvement (Jorm, 1986).

In recent years, the concept of a single attentional resource pool has tended to be replaced by multiple resource theory, which assumes a number of specialized pools of processing resources, that may act either independently or in concert, depending on task demands (Wickens, 1984). It is usual for multiple resource models to assume that when 2 tasks must be performed at the same time, there is a 'cost of concurrence' (Navon and Gopher, 1979). One way of interpreting this cost is to assume that dual task coordination requires some form of central attentional processing module, what Hunt and Lansman (1982) refer to as an 'executive time sharer'.

The working memory model is of course a multiple resource system in which executive time-sharing is assumed to be dependent on the central executive. It has the advantage over more generally specified multiple resource models, such as that of Wickens (1984), of attempting to specify the constituent modules in more detail and of linking them closely to neuropsychological evidence (Baddeley, 1986, 1990).

In the case of the central executive, the neuropsychological link has been facilitated by adopting the Norman and Shallice (1980) model of attentional control, which Shallice (1982) has used to interpret the cognitive deficits found in the frontal lobe syndrome. The model assumes that most ongoing actions are controlled by establishing routines, with contention-scheduling procedures operating automatically to minimize conflict between concurrent well-learned skills such as talking and driving. The system is assumed to be monitored by a Supervisory Attentional System (SAS) which is able to override ongoing activities when necessary, for instance when a driver might stop a conversation to ask the way.

Shallice (1982, 1988) suggests that the frontal syndrome (Goldberg and Bilder, 1987; Stuss and Benson, 1987) may reflect damage to the operation of the SAS, leading to problems in the attentional control of behaviour. This produces both perseveration, when the SAS fails to break into the ongoing activity when appropriate, and distractability, when the SAS fails to maintain the desired activity in the face of other distracting sources of information (Shallice *et al.*, 1989). While a full account of both normal attentional control and of the frontal syndrome will clearly demand a more detailed theory, the model has proved useful in further investigating frontal deficits (Shallice, 1982, 1988; Baddeley and Wilson, 1988; Shallice *et al.*, 1989). In the case of AD, we and others have suggested that the capacity to direct and control attentional resources may be one of the principal cognitive deficits observed (Baddeley *et al.*, 1986; Becker, 1988; Morris and Baddeley, 1988; Cossa *et al.*, 1989; Spinnler, 1991). While the working memory model is not the only way of conceptualizing such a deficit, it has so far provided a convenient and fruitful framework for investigating the nature of the observed cognitive decline.

We have described 2 group studies which we have so far discussed as if they reflect a uniform pattern of performance deficits. This is not of course the case for our sample or, we suspect, for any sample of AD patients. The heterogeneity of cognitive deficits found among carefully diagnosed AD patients has often been documented (Capitani *et al.*, 1986; Della Sala *et al.*, 1986; Martin *et al.*, 1986; Becker, 1988; Spinnler and

Della Sala, 1988), and was observed within the group of patients from which the present sample were drawn (Baddeley *et al.*, 1991). Patients were found to differ quite widely in their precise pattern of cognitive deficits, with occasional patients having relatively pure and isolated areas of impairment, although other deficits would typically appear in such patients as the disease progressed. The fact that group studies are able to show an apparently coherent pattern of impairment presumably reflects the fact that certain deficits are particularly prevalent and marked in AD patients, possibly reflecting the nature and distribution of the underlying pathological processes.

We are aware that this deficit may not be unique to AD. It might well be that other conditions resulting from brain damage lead to similar impairments. Nonetheless, in terms of sensitivity to the progress of the disease, our dual task measures appear to have considerable advantages. Our earlier study (Baddeley *et al.*, 1986) has shown that they are sensitive in discriminating the effects of AD from the normal processes of ageing, suggesting that they may provide good measures for both detecting AD and monitoring its progress. This is in agreement with findings reported by other researchers on normal ageing (Wright, 1981; Light and Anderson, 1985; Gick *et al.*, 1988; Morris *et al.*, 1988, 1990) which suggested that normal ageing does not lead *per se* to a substantial impairment of the time-sharing component of working memory. The current experimental procedure is, however, somewhat inconvenient logistically, and we therefore plan to develop and validate a version that will be more suitable for clinical practice.

REFERENCES

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders, DSM-III-R. Third edition-Revised.* Washington, DC: American Psychiatric Association, pp. 103–123.

Baddeley AD (1986) *Working Memory.* Oxford: Clarendon Press.

Baddeley AD (1990) *Human Memory: Theory and Practice.* London: Lawrence Erlbaum.

Baddeley AD, Warrington EK (1970) Amnesia and the distinction between long- and short-term memory. *Journal of Verbal Learning and Verbal Behavior,* **9**, 176–189.

Baddeley AD, Hitch GJ (1974) Working memory. In: *Recent Advances in Learning and Motivation,* Volume III. Edited by G. Bower. London: Academic Press, pp. 47–90.

Baddeley AD, Lieberman K (1980) Spatial working memory. In. *Attention and Performance VIII.* Edited by R. S. Nickerson. Hillsdale, NJ: Lawrence Erlbaum, pp. 521–539.

Baddeley A, Lewis V, Eldridge M, Thomson N (1984) Attention and retrieval from long-term memory. *Journal of Experimental Psychology: General,* **113**, 518–540.

Baddeley A, Logie R, Bressi S, Della Sala S, Spinnler H (1986) Dementia and working memory. *Quarterly Journal of Experimental Psychology,* **38A**, 603–618.

Baddeley AD, Wilson B (1988) Frontal amnesia and the dysexecutive syndrome. *Brain and Cognition,* **7**, 212–230.

Baddeley A, Della Sala S, Spinnler H (1991) The two-component hypothesis of memory deficit in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology,* **13**, 372–380.

Battig WF, Montague WE (1969) Category norms for verbal items in 56 categories: a replication and extension of the Connecticut Category Norms. *Journal of Experimental Psychology Monograph,* **80**, Number 3, Part 2, 1–46.

Becker JT (1988) Working memory and secondary memory deficits in Alzheimer's disease. *Journal of Clinical and Experimental Neuropsychology,* **10**, 739–753.

Benton AL, Van Allen MW, Fogel ML (1964) Temporal orientation in cerebral disease. *Journal of Nervous and Mental Disease,* **139**, 110–119

Butters N, Stuss AT (1989) Diencephalic amnesia. In: *Handbook of Neuropsychology,* Volume 3. Edited by F. Boller and J. Grafman. Amsterdam: Elsevier, pp. 107–148.

Canter GJ, de La Torre R, Mier M (1961) A method for evaluating disability in patients with Parkinson's disease. *Journal of Nervous and Mental Disease*, **133**, 143–147.

Capitani E, Della Sala S, Spinnler H (1986) Neuropsychological approach to dementia. In: *Neurology*. Edited by K. Poeck, H. J. Freund and H. Gaensehirt. Heidelberg: Springer, pp. 61–69.

Chertkow H, Bub D (1990) Semantic memory loss in dementia of Alzheimer's type: what do various measures measure? *Brain*, **113**, 397–417.

Corkin S (1982) Some relationships between global amnesias and the memory impairments in Alzheimer's disease. In: *Alzheimer's Disease: A Report of Progress in Research*. Edited by S. Corkin, K. L. Davis, J. H. Growdon, E. Usdin and R. J. Wurtman. New York: Raven Press, pp. 149–164.

Cossa FM, Della Sala S, Spinnler H (1989) Selective visual attention in Alzheimer's and Parkinson's patients: memory- and data-driven control. *Neuropsychologia*, **27**, 887–892.

Craik FIM (1984) Age differences in remembering. In: *Neuropsychology of Memory*. Edited by L. R. Squire and N. Butters. New York and London: Guilford Press, pp. 3–12.

Dall'Ora P, Della Sala S, Spinnler H (1989) Autobiographical memory. Its impairment in amnesic syndromes. *Cortex*, **25**, 197–217.

de Leon MJ, George AE (1983) Computed tomography in aging and senile dementia of the Alzheimer type. *Advances in Neurology*, **38**, 103–122.

Della Sala S, Nespoli A, Ronchetti E, Spinnler H (1984) Does chronic liver failure lead to chronic mental impairment? In: *Advances in Hepatic Encephalopathy and Urea Cycle Diseases*. Basel: Karger, pp. 448–456.

Della Sala S, Nichelli P, Spinnler H (1986) An Italian series of patients with organic dementia. *Italian Journal of Neurological Sciences*, **7**, 27–41.

De Renzi E, Faglioni P (1978) Normative data and screening power of a shortened version of the Token Test. *Cortex*, **14**, 41–49.

Eslinger PJ, Damasio H, Graff-Radford N, Damasio AR (1984) Examining the relationship between computed tomography and neuropsychological measures in normal and demented elderly. *Journal of Neurology, Neurosurgery, and Psychiatry*, **47**, 1319–1325.

Farmer EW, Berman JVF, Fletcher YL (1986) Evidence for a visuo-spatial scratch-pad in working memory. *Quarterly Journal of Experimental Psychology*, **38A**, 675–688.

Gick ML, Craik FIM, Morris RG (1988) Task complexity and age differences in working memory. *Memory and Cognition*, **16**, 353–361.

Goldberg E, Bilder RM (1987) The frontal lobes and hierarchical organization of cognitive control. In: *The Frontal Lobes Revisited*. Edited by E. Perecman. New York: IRBN Press, pp. 159–187.

Hunt E, Lansman M (1982) Individual differences in attention. In: *Advances in the Psychology of Human Intelligence*, Volume 1. Edited by R. J. Sternberg. Hillsdale, NJ: Lawrence Erlbaum, pp. 207–254.

Jorm AF (1986) Controlled and automatic information processing in senile dementia: a review. *Psychological Medicine*, **16**, 77–88.

Kahneman D (1973) *Attention and Effort*. Englewood Cliffs, NJ: Prentice-Hall.

Kopelman MD (1985) Rates of forgetting in Alzheimer-type dementia and Korsakoff's syndrome. *Neuropsychologia*, **23**, 623–638.

Kopelman MD (1989) Remote and autobiographical memory, temporal context memory and frontal atrophy in Korsakoff and Alzheimer patients. *Neuropsychologia*, **27**, 437–460.

Light LL, Anderson PA (1985) Working-memory capacity, age, and memory for discourse. *Journal of Gerontology*, **40**, 737–747.

Logie RH, Zucco GM, Baddeley AD (1990) Interference with visual short-term memory. *Acta Psychologica*, **75**, 55–74.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology, Cleveland*, **34**, 939–944.

Martin A, Brouwers P, Lalonde F, Cox C, Teleska P, Fedio P *et al.* (1986) Towards a behavioral typology of Alzheimer's patients. *Journal of Clinical and Experimental Neuropsychology*, **8**, 594–610

Miller E (1973) Short- and long-term memory in patients with presenile dementia (Alzheimer's disease). *Psychological Medicine*, **3**, 221–224.

Miller E (1977) *Abnormal Ageing: The Psychology of Senile and Presenile Dementia*. London: John Wiley.

MILNER B (1966) Amnesia following operation on the temporal lobes. In: *Amnesia*. Edited by C. W. M. Whitty and O. L. Zangwill. London: Butterworths, pp. 109–133.

MORRIS RG (1984) Dementia and the functioning of the articulatory loop system. *Cognitive Neuropsychology*, **1**, 143–157.

MORRIS RG (1986) Short-term forgetting in senile dementia of the Alzheimer's type. *Cognitive Neuropsychology*, **3**, 77–97.

MORRIS RG, BADDELEY AD (1988) Primary and working memory functioning in Alzheimer-type dementia. *Journal of Clinical and Experimental Neuropsychology*, **10**, 279–296.

MORRIS RG, GICK ML, CRAIK FIM (1988) Processing resources and age differences in working memory. *Memory and Cognition*, **16**, 362–366.

MORRIS RG, CRAIK FIM, GICK ML (1990) Age differences in working memory tasks: the role of secondary memory and the central executive system. *Quarterly Journal of Experimental Psychology*, **42A**, 67–86.

MURDOCK BB (1965) Effects of a subsidiary task on short-term memory. *British Journal of Psychology*, **56**, 413–419.

NAUGLE RI, BIGLER ED (1989) Brain imaging and neuropsychological identification of dementia of the Alzheimer's type. In: *Neuropsychological Function and Brain Imaging*. Edited by E D. Bigler, R. A. Yeo and E. Turkheimer. New York and London: Plenum Press, pp. 185–218.

NAVON D, GOPHER D (1979) On the economy of the human-processing system. *Psychological Review*, **86**, 214–255.

NORMAN DA, SHALLICE T (1980) *Attention to Action: Willed and Automatic Control of Behavior*. CHIP Report 99. San Diego: University of California.

NORMAN DA, SHALLICE T (1986) Attention and action: willed and automatic control of behavior. In: *Consciousness and Self-regulation*, Volume 4. Edited by R. J. Davidson, G. E. Schwartz and D. Shapiro. New York and London: Plenum Press, pp. 1–18.

RAVEN JC (1938) *Standard Progressive Matrices. Sets A, B, C, D.* London: H. K. Lewis.

SCHNEIDER W, SHIFFRIN RM (1977) Controlled and automatic human information processing: I. Detection, search, and attention. *Psychological Review*, **84**, 1–66.

SHALLICE T (1982) Specific impairments of planning. *Philosophical Transactions of the Royal Society of London, B*, **298**, 199–209.

SHALLICE T (1988) *From Neuropsychology to Mental Structure*. Cambridge: Cambridge University Press.

SHALLICE T, BURGESS PW, SCHON F, BAXTER DM (1989) The origins of utilization behaviour. *Brain*, **112**, 1587–1598.

SPINNLER H (1991) The role of attention disorders in the cognitive breakdown of dementia. In: *Handbook of Neuropsychology*, Volume 5. Edited by F. Boller and J. Grafmann. Amsterdam. Elsevier. In press.

SPINNLER H, TOGNONI G (1987) Taratura e standardizzazione italiana di test neuropsicologici. *Italian Journal of Neurological Sciences*, **8**, Supplement 8, 8–120.

SPINNLER H, DELLA SALA S (1988) The role of clinical neuropsychology in the neurological diagnosis of Alzheimer's disease. *Journal of Neurology*, **235**, 258–271.

SPINNLER H, DELLA SALA S, BANDERA R, BADDELEY A (1988) Dementia, ageing, and the structure of human memory. *Cognitive Neuropsychology*, **5**, 193–211.

STREET RF (1931) *A Gestalt Completion Test*. New York: Teachers' College Press.

STUSS AT, BENSON DF (1987) The frontal lobes and control of cognition and memory. In: *The Frontal Lobe Revisited*. Edited by E. Perecman. New York: IRBN Press, pp. 141–158.

VALLAR G, SHALLICE T (1990) *Neuropsychological Impairments of Short-term Memory*. Cambridge: Cambridge University Press.

WARRINGTON EK (1982) The double dissociation of short- and long-term memory deficits. In: *Human Memory and Amnesia*. Edited by L. S. Cermak. Hillsdale, NJ: Lawrence Erlbaum, pp. 61–76.

WARRINGTON EK, WEISKRANTZ L (1970) Amnesic syndrome: consolidation or retrieval? *Nature, London*, **228**, 628–630.

WICKENS CD (1984) Processing resources in attention. In: *Varieties of Attention*. Edited by R. Parasuraman and D. R. Davies. Orlando, FL: Academic Press, pp. 63–102.

WILCOCK GK, HOPE RA, BROOKS DN, LANTOS PL, OPPENHEIMER C, REYNOLDS GP *et al.* (1989) Recommended minimum data to be collected in research studies on Alzheimer's disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, **52**, 693–700.

WILSON BW, BADDELEY AD (1988) Semantic, episodic and autobiographical memory in a postmeningitic patient. *Brain and Cognition*, **8**, 31–46.

WILSON RS, BACON LD, FOX JH, KASZNIAK AW (1983) Primary memory and secondary memory in dementia of the Alzheimer type. *Journal of Clinical Neuropsychology*, **5**, 337–344.

WRIGHT RE (1981) Aging, divided attention, and processing capacity. *Journal of Gerontology*, **36**, 605–614.

YNTEMA DB (1963) Keeping track of several things at once. *Human Factors*, **5**, 7–17.

ZANGWILL OL (1946) Some qualitative observations on verbal memory in cases of cerebral lesion. *British Journal of Psychology*, **37**, 8–19.

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Brain (1991), **114**, 2543–2554

INSPECTION TIME, PSYCHOMETRIC INTELLIGENCE AND CLINICAL ESTIMATES OF COGNITIVE ABILITY IN PRE-SENILE ALZHEIMER'S DISEASE AND KORSAKOFF'S PSYCHOSIS

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SUMMARY

Ten pre-senile Alzheimer's patients, 11 patients with Korsakoff's psychosis and 11 age- and pre-morbid intelligence-matched controls were given a test of Inspection Time, which estimates the efficiency of visual encoding or iconic memory. Alzheimer's patients had impaired Inspection Time while the Korsakoff group performed very similarly to the controls. Inspection Time performance correlated significantly with psychometric tests of cognitive ability and with clinical tests of cognitive ability (Mini Mental State Examination and Cambridge Mental Disorders of the Elderly Examination). The early stage of information processing measured by the Inspection Time procedure appears to be damaged by the Alzheimer's disease process, and to impose a rate-limiting effect on a wide variety of mental tests.

INTRODUCTION

Recent advances in the understanding of the psychological deficits in the dementias have come from the application of information processing principles to the cognitive tests which are used to assess degrees of cognitive decline. For instance, the work of Kopelman (1985*a*,*b*) has demonstrated that short-term memory capacity and forgetting are impaired in Alzheimer's disease but not in Korsakoff's syndrome, whereas the ability to aquire new information into long-term memory is reduced in both of these disorders. Although most experimental studies focus upon short- and long-term memory problems, there is some evidence to indicate that patients with Alzheimer's disease and Korsakoff's syndrome have deficits at an earlier stage of information processing (Oscar-Berman *et al.*, 1973; Schlotterer *et al.*, 1983). Typically, they are found to be poorer than control subjects in correctly identifying briefly presented visual stimuli. This deficit involves a stage of information processing which is the earliest and, to most psychiatrists and many psychologists, the least familiar of the memory 'stores'. Sometimes called iconic memory (or the sensory store; Neisser, 1967; Sperling, 1967), it is a large-capacity, fast-decaying temporary register of perceptual information, some of which may be passed to the short-term (or 'working' memory) to be used as information for conscious decision making.

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Experiments on the visual encoding of information involve very brief presentations of stimuli (often around 100 ms or less), such as upper-case letters, using a tachistoscope or a computer screen. Normally the key independent variable is the presentation time required by the subject to identify the stimulus accurately. Such a high contrast but briefly-presented stimulus leaves an after image, which allows further processing of the stimulus to take place. Therefore, stimulus offset is followed by a backward mask. Backward masking prevents post-stimulus processing, and takes two forms. In contrast masking a homogenous bright white light may follow a stimulus. In the case of pattern masking the stimulus offset is followed by a figure which has similar contours. For details of the experiments which led to the differentiation of contrast masking, a peripheral phenomenon, and pattern masking, *see* Turvey (1973). That pattern masking is a central process, not dependent upon factors which are important in peripheral masking such as relative luminance of stimulus and mask, has been demonstrated in several experiments where it has been shown that backward pattern-masking effects continue to exist when the stimulus and mask are presented to separate eyes or visual fields (Turvey, 1973; Nettelbeck and McLean, 1984; Nettelbeck *et al.*, 1984).

In a visual masking experiment where the stimuli were alphabetic characters, patients with Alzheimer's disease required longer presentation times when compared with age-matched controls in order to make accurate judgements in a pattern mask condition, but were no different from controls in a homogenous 'flash' mask condition (Schlotterer *et al.*, 1983). Ageing controls required longer presentation times for stimulus identification than young controls in both masking conditions. The authors concluded that, 'these results strongly suggest that the speed of central visual processes that normally slows down with age is reduced even further in Alzheimer's disease'. Oscar-Berman *et al.* (1973) showed that patients with Korsakoff's syndrome had longer visual processing time requirements than both alchoholic and normal controls, especially for verbal material. They concluded that, '. . . our results show that Korsakoff patients require more than normal amounts of time for the processing of visual information. These findings have important implications for studies where Korsakoff encoding or retrieval "deficits" may be confounded with inadequate stimulus input opportunity'. However, in the above studies the control group may have been inadequately matched to the clinical group. In the study by Oscar-Berman *et al.* (1973) the non-Korsakoff's alcoholic and normal control groups were considerably younger than the Korsakoff's group. In the Schlotterer *et al.* (1983) report there was no mention of the control and Alzheimer's groups being matched for pre-morbid intelligence. Since both age and intelligence are related to visual processing indices (Nettelbeck, 1987) they must be considered as potentially confounding variables which prevent the above studies being definitive. Further, both studies used the psychophysical method of ascending limits which, as we discuss below, may be unsuitable for patients with cognitive impairment.

The test of visual encoding used in the present study is 'Inspection Time'. Unlike most tests of iconic processing, Inspection Time was not developed by experimental or cognitive psychologists. Instead, it arose out of psychophysical theory (Vickers *et al.*, 1972; Vickers and Smith, 1986). The background to the measure is the notion that the environment is sampled by perceptual processes in quanta called 'inspections'. The presentation time required by a subject in order to make an accurate two-choice decision on a simple stimulus is called the 'Inspection Time' of that individual for the particular stimulus. Inter-individual differences in Inspection Time are stable, and there is some evidence to indicate that Inspection Time ages like other physical capacities, with a peak in early adulthood (Nettelbeck, 1987).

The most commonly used Inspection Time stimulus is two parallel vertical lines of markedly different lengths. Following the presentation of the stimulus the subject is required to indicate which of the lines was longer. The backward pattern mask consists of two thicker, longer lines of equal length which completely overlie the stimulus. The large difference in the stimulus line lengths means that the discrimination is extremely easy and does not tap individual differences in visual acuity. The task is made more difficult by shortening the duration of the stimulus prior to mask onset. Inspection Time is not a reaction time test—subjects' responses are made in their own time and the only aspect of their response which is recorded is the correctness. Individual differences in Inspection Time correlate at moderate levels (the average corrected correlation is around −0.5) with tests of psychometric intelligence (brighter subjects have lower inspection times). The relationship holds for normal adults, students and children, and the correlations are higher when mentally handicapped subjects are tested (Brand and Deary, 1982; Nettelbeck, 1987). The ease of Inspection Time discrimination makes it a suitable test with which to study the visual encoding of patients with cognitive deficits, given its success in several studies with mentally handicapped individuals (Nettelbeck, 1987).

In summary, Inspection Time was assessed along with clinical cognitive tests and psychometric IQ-type tests in groups of patients with Alzheimer's disease and Korsakoff's syndrome in the present study because: (*a*) Inspection Time measures appear to tap early visual processing, which has been relatively neglected in these groups; (*b*) the Inspection Time measure takes the form of a simple discrimination resulting in a continuous variable which is appropriate to the identification of disease progression and treatment effects; (*c*) the relationship of Inspection Time to other clinical measures of cognitive function in dementia is of interest because of the emphasis given to these in the diagnosis and investigation of these patients.

SUBJECTS AND METHODS

The study was approved by the appropriate medical ethics committee. Informed consent to take part in the study was obtained from patients and, where appropriate, nearest relatives in accordance with the Declaration of Helsinki.

Subjects

Patients with Alzheimer's disease and Korsakoff's syndrome were unselected referrals to a unit seeking such referrals from local neurological and psychiatric services.

Alzheimer-type dementia. Thirteen patients with a clinical diagnosis of pre-senile Alzheimer's disease were referred to the study. Only those patients who had adequate visual acuity and who were cognitively competent enough to respond reliably in the Inspection Time test were studied further. This left 10 patients who met the following criteria which indicate a probable diagnosis of pre-senile Alzheimer's disease (McKhann *et al.*, 1984): (*a*) onset of symptoms before the age of 65 yrs with dysmnesia as the initial feature; (*b*) steadily progressing dementia; (*c*) no history to suggest other types of dementia; (*d*) absence of focal neurological signs; (*e*) no evidence of hypertension or other cardiovascular abnormalities; (*f*) CT scan normal or showing only cerebral atrophy with no additional pathology; (*g*) no focal EEG abnormalities; (*h*) normal haematological, biochemical and CSF clinical investigations.

Alcoholic Korsakoff's syndrome. Twelve patients were referred to the study. Eleven patients had adequate visual acuity, completed the Inspection Time test and met the following diagnostic criteria indicating a probable diagnosis of Korsakoff's syndrome: (*a*) definite history of alcohol abuse, usually in excess of 20 yrs; (*b*) severe anterograde memory deficit; (*c*) no history of progressive dementia; (*d*) definite history of past episodes of either acute confusion of Wernicke's encephalopathy (with or without peripheral neuropathy); (*e*) EEG showing no focal abnormality; (*f*) normal haematological and biochemical tests; (*g*) no alcoholic beverage taken for at least 6 mths.

Control subjects. Eleven control subjects were recruited with the aim of providing a group which was similar to both of the patients groups in age and pre-morbid intelligence level. All had adequate visual acuity and completed the Inspection Time test.

None of the patients or control subjects had taken psychotropic medication in the 6 mths before testing.

Psychometric and psychophysical testing

All three groups (Alzheimer, Korsakoff and Control) completed the National Adult Reading Test, the Cattell Culture Fair Test of Intelligence Form 2A, Digit Symbol Substitution Test from the Wechsler Adult Intelligence Scale—Revised (WAIS-R) and the Inspection Time task. In addition, patients with Alzheimer's disease and Korsakoff's syndrome completed the Mini Mental State Examination and the cognitive testing section of the Cambridge Mental Disorders of the Elderly Examination.

National Adult Reading Test (Nelson and O'Connell, 1978). This test gives an estimate of the intelligence level of normal subjects, and an estimate of the pre-morbid intelligence level of subjects suffering from cognitive deterioration. National Adult Reading Test IQ estimates correlate very highly with WAIS and WAIS-R measured IQs in normal subjects, and are superior to demographic variables in estimating pre-morbid IQ in cognitively impaired subjects (Crawford, 1989; Crawford *et al.*, 1989). The test involves the subjects attempting to pronounce 50 irregular English words.

Cattell Culture Fair Test of Intelligence, Form 2A (Cattell, 1957). This gives an estimate of non-verbal 'fluid' intelligence. It is a timed test with 4 subtests, all of which demand that the subject studies novel abstract material and infers rules from presented examples in order to choose the correct alternative from a number of answer options.

Digit Symbol Substitution Test (Wechsler, 1981). This is a performance subtest from the Wechsler Adult Intelligence Scale—Revised. As such, it has a closer relationship to 'fluid' than to 'crystallized' (vocabularly-oriented) intelligence.

Mini Mental State Examination (Folstein *et al.*, 1975). This is a brief test which is composed of items relating to orientation, memory, language and visuo-spatial ability. Performance on the test is expressed as a total score.

Cambridge Mental Disorders of the Elderly Examination (Roth *et al.*, 1986). This test, which was developed in order to diagnose and to assess quantitatively dementia, has a cognitive testing section, which contained 14 of the 19 Mini Mental State Examination items plus 43 additional items. Its performance may be expressed in terms of a total score or a subscale score. The subscales are: Orientation; Comprehension and Expression, which may be combined to give a Language score; Remote Memory, Recent Memory and Learned Memory, which may be combined to give a Total Memory score; Attention; Praxis; Calculation; Abstraction; and Perception.

Inspection Time. The visual Inspection Time test used in the present study was similar to that devised by Deary *et al.* (1989). The two-choice discrimination involved the subject in indicating, by pointing at a computer monitor screen or responding verbally, which of two parallel vertical lines of markedly different lengths was longer. Stimuli and mask were presented using a screen luminance of 2800 lux ca. on a background of 44 lux ca. The long stimulus line was 14 mm and the short line was 6 mm. The lines were set 10 mm apart, and they were approximately 1 mm wide The backward visual pattern mask was a pair of identical vertical lines 19 mm long and 3.5 mm wide, which completely covered the stimulus area after stimulus offset. Subject's eyes were 60 cm from the computer screen. Before each stimulus a cue lasted 500 ms and there was a 1000 ms cue-stimulus gap. As is typical of Inspection Time testing, there was no Stimulus-Mask Interval, the mask was presented immediately after stimulus offset, which avoids problems of stimulus persistence due to the decay time of the screen phosphor. The mask lasted for 500 ms. Inter-trial interval was about 4 s, but the test was essentially self-paced because subjects could take as much time as they required before responding. A response started the next trial. Only the correctness of the subject's response was recorded. No reaction time was taken and subjects were repeatedly encouraged to respond at leisure and with maximum accuracy.

The dependent variable obtained from the Inspection Time test (the subject's estimated 'inspection time') is the stimulus presentation time (in ms) which a subject requires in order to obtain 85% correct responses (50% representing chance responding). The 85% point on the subject's psychometric curve is determined by altering the stimulus presentation time according to the Parameter Estimation by Sequential Testing adaptive staircase algorithm (Taylor and Creelman, 1967). In the version of the algorithm used in this study the starting stimulus duration was 400 ms and the first step size was 75 ms. The duration change was halved with each reversal in the staircase. The criterion for stopping the algorithm was the achievement of a duration change size of 1 ms. There was no set number of trials to be completed, but the minimum number of trials required to finish the procedure was about 50. The mean number of presentations was about 100, as is typical for the Parameter Estimation by Sequential Testing. The Inspection Time test was controlled by a BBC microcomputer. The time for completion of this procedure was variable, depending on the number of trials needed to achieve the criterion, but the range was from about 12 min to about 30 min with a mean of about 18 min.

As is indicated above, using the Parameter Estimation by Sequential Testing algorithm rather than a set number of trials results in the number of test items and the session length being variable across subjects. In essence, Parameter Estimation by Sequential Testing uses reliability of response as its stopping criterion, and we consider this to be of great importance when testing cognitively impaired individuals on psychophysical tests. There is a danger that such patients might make a poor start on the test (because of the general novelty of the set-up or because they are slow to pick up the idea of the task), or they might lose concentration and begin to respond at random. Because Inspection Time involves a two-choice discrimination with a 50% chance of giving a correct response, it is always possible to assign a score of some kind when a set number of trials has been presented to the subject. However, we required the subjects to complete the Parameter Estimation by Sequential Testing algorithm before being assigned an 'Inspection Time'. We reasoned that, since those subjects have completed the algorithm, their Inspection Time is a meaningful index of visual information intake efficiency. As far as can be ascertained from the descriptions of methodology in previous studies of the iconic storage of Alzheimer and Korsakoff patients (Oscar-Berman *et al.*, 1973; Miller, 1977; Schlotterer *et al.*, 1983), the above precautions were not taken.

Statistical analysis

One-way ANOVA testing was used to compare the results of those tests taken by all three groups. When pairs of groups were tested independent *t* tests were used. Pearson's *r* was used for the intercorrelation of test results both within each clinical group and for larger groups formed by the joining together of individual groups. One subject with Alzheimer's disease had no Digit Symbol Substitution Test, and one subject with Korsakoff's syndrome had no Cattell IQ test. One subject with Alzheimer's disease and 2 subjects with Korsakoff's syndrome had no Cambridge Mental Disorders of the Elderly Examination—cognitive section test. Therefore, statistical analyses often involve slightly different numbers. Because the missing data are few, the number variations have not been detailed in the tables, but the *P* values have been calculated using the appropriate degrees of freedom.

RESULTS

Table 1 contains descriptive statistics for the three groups on all dependent variables. The groups were very similar in age and pre-morbid intelligence. On tests of 'fluid' cognitive ability, Cattell Culture Fair Test of Intelligence, Form 2A and Digit Symbol Substitution Test, there were clear differences among the groups on one-way ANOVA. In both tests the Alzheimer's group scored lowest and the control group highest, with the Korsakoff's group in between. *Post hoc* testing using independent *t* tests (there was no requirement for other tests because there were only three groups, very few *post hoc* tests were performed and the differences were large) revealed that the Alzheimer's and Korsakoff's groups differed significantly on Cattell Culture Fair Test of Intelligence, Form 2A ($t = 3.30$, $P = 0.005$) and Digit Symbol Substitution Test ($t = 2.83$, $P = 0.01$). Control and Korsakoff groups also differed significantly on Cattell Culture Fair Test of Intelligence, Form 2A ($t = 2.73$, $P = 0.01$) and Digit Symbol Substitution

TABLE 1 SUMMARY DATA AND RESULTS OF STATISTICAL COMPARISONS FOR THE THREE GROUPS STUDIED.

	Alzheimer	*Korsakoff*	*Control*	*Statistical test results*
n	10	11	11	
Age	60.7 (4.1)	59.6 (6.7)	59.2 (4.0)	F = 0.24, ns
NART	28.3 (10.2)	23.8 (12.6)	27.4 (9.3)	F = 0.49, ns
CCF	9.1 (6.9)	18.3 (5.1)	25.6 (7.3)	F = 16.00, $P < 0.001$
DSST	10.2 (12.5)	24.7 (9.7)	43.5 (9.0)	F = 26.59, $P < 0.001$
CAMDEX-Cog	62.1 (13.4)	78.0 (14.6)	—	t = 2.41, $P = 0.029$
MMSE	15.3 (4.6)	21.3 (5.6)	—	t = 2.61, $P = 0.018$
Inspection Time	157.3 (62.9)	96.5 (53.3)	93.2 (42.9)	F = 4.72, $P = 0.017$

NART = National Adult Reading Test, CCF = Cattell Culture Fair Intelligence Test, Form 2A; DSST = Digit Symbol Substitution Test from the WAIS-R, CAMDEX-Cog = cognitive score from CAMDEX test; MMSE = Mini Mental State Examination.

Test ($t = 4.46$, $P < 0.001$). Table 1 shows that the Korsakoff group scored significantly higher than the Alzheimer patients on the Cambridge Mental Disorders of the Elderly Examination—cognitive section and Mini Mental State Examination tests.

With regard to the study's key variable, one-way ANOVA testing also showed a significant difference among groups on Inspection Time (Table 1). *Post hoc* testing showed that the Alzheimer's group differed significantly from both the Korsakoff's ($t = 2.38$, $P = 0.03$) and the Control group ($t = 2.70$, $P = 0.02$), whereas the latter two groups were very similar ($t = 0.16$, ns).

Table 2 contains the correlations between Inspection Time scores and the scores on psychometric and clinical tests of cognitive ability. These have been calculated for each group separately and for combined Alzheimer's+Korsakoff's and Alzheimer's+Korsakoff's+Control groups. The latter two group combinations are valid because scattergrams revealed reasonable overlaps between groups on all test scores, i.e. the correlations based on combined groups were not due to the individual groups acting as extreme points on the regression line (Figs 1, 2 are typical scattergrams and show the relationships between Cattell Culture Fair Test scores and Inspection Time and Cambridge Mental Disorders of the Elderly Examination—cognitive section, respectively). There were no significant correlations between Inspecton Time and age. Inspection

TABLE 2. PEARSON (r) CORRELATIONS BETWEEN INSPECTION TIME AND PSYCHOMETRIC AND CLINICAL TESTS OF MENTAL ABILITY WITHIN THE THREE GROUPS AND IN COMBINATIONS OF THE GROUPS (DECIMAL POINTS OMITTED FROM COEFFICIENTS)

	Age	*NART*	*CCF*	*DSST*	*CAMDEX-Cog*	*MMSE*
Control	−08	−66*	−55	−63*	—	—
Alzheimer	−12	+58	−59	−74**	−81**	−44
Korsakoff	−09	−42	−32	−14	−33	−26
Alzheimer+Korsakoff	−00	+15	−63***	−65***	−67***	−49*
Alzheimer+Korsakoff+ Control	−02	−05	−62****	−64****	—	—

* = $P < 0.05$; ** = $P < 0.02$; *** = $P < 0.01$; **** = $P < 0.001$; NART = National Adult Reading Test, CCF = Cattell Culture Fair Intelligence Test, Form 2A; DSST = Digit Symbol Substitution Test from the WAIS-R, CAMDEX-Cog = cognitive score from CAMDEX test; MMSE = Mini Mental State Examination.

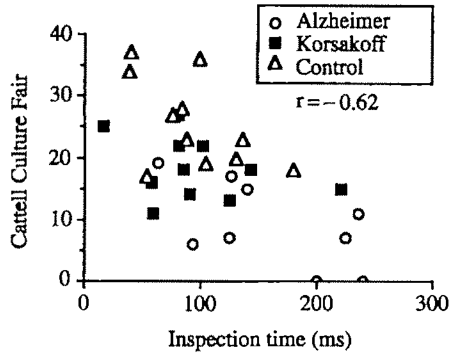

FIG. 1 Scattergram showing the relationship between Inspection Time and Cattell Culture Fair score for the Combined Alzheimer+Korsakoff+Control group

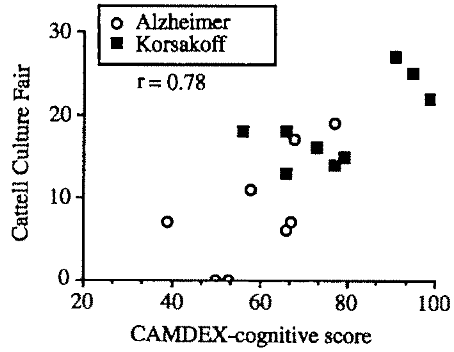

FIG. 2. Scattergram showing the relationship between Cattell Fair score and Cambridge Mental Disorders of the Elderly Examination—cognitive score for the combined Alzheimer+Korsakoff group.

Time and National Adult Reading Test scores correlated significantly only for the control group. In the Korsakoff group, where cognitive ability is relatively preserved, the Inspection Time/National Adult Reading Test correlation is in the expected direction, but non-significant. For the Alzheimer's group, where global cognitive change leads to the expectation that there will be little correlation between present and pre-morbid IQ, and where Inspection Time has been impaired by the disease process, the correlation is in the opposite direction, but is non-significant. Correlations between National Adult Reading Test and non-verbal measures of ability also confirmed the loss of premorbid IQ to present IQ correlation in the Alzheimer's group. Within the control group the National Adult Reading Test vs Cattell Culture Fair Test of Intelligence, Form 2A and Digit Symbol Substitution Test correlations were both 0.78 ($P < 0.01$), whereas the respective correlations within the Alzheimer group were −0.42 (ns) and −0.60 (P approx. 0.05), and within the Korsakoff's group were 0.41 (ns) and 0.83 ($P < 0.01$).

All correlations between Inspection Time and clinical and 'fluid' cognitive tests were in the expected direction (Table 2). Within each group Cattell Culture Fair Test of Intelligence, Form 2A and Inspection Time correlated in the expected direction at moderate levels, but the correlations only achieved significance when the groups were combined. Digit Symbol Substitution Test scores correlated significantly with Inspection Time in both the control and Alzheimer's groups, and in combined groups. Cambridge Mental Disorders of the Elderly Examination—cognitive section correlated significantly with Inspection Time in the Alzheimer's group and in the combined Alzheimer's+ Korsakoff's group. The Mini Mental State Examination correlated significantly with Inspection Time in the combined clinical group.

The correlations between Inspection Time and the Cambridge Mental Disorder of the Elderly Examination—cognitive section subscales (excluding subtotals which are simple sums of subtests) were computed for the Alzheimer's and Korsakoff's groups separately and for the combined Alzheimer's+Korsakoff's group. All except 4 of the 33 correlations (but note that not all of these were independent correlations because the same patients appear in the separate and combined clinical groups) were in the expected direction, and the exceptions were small, non-significant correlations, mostly between 0 and 0.1. The mean correlation between Inspection Time and the 11 Cambridge Mental Disorders of the Elderly Examination—cognitive section subtests was -0.51 in the Alzheimer's group, where 5 of the 11 correlations between Inspection Time and Cambridge Mental Disorders of the Elderly Examination—cognitive section subtests were significant at $P < 0.05$ (for Comprehension, Expression, Remote Memory, Praxis and Calculation). In the combined Alzheimer's+Korsakoff's group all of the Inspection Time/Cambridge Mental Disorders of the Elderly Examination—cognitive section correlations were in the expected direction, and 6 of the 11 correlations with individual subtests were significant at $P < 0.05$ (for Comprehension, Expression, Remote Memory, Praxis, Calculation and Perception).

Both the Cattell Culture Fair Test of Intelligence, Form 2A and the Digit Symbol Substitution Test correlated at high levels with the clinical tests of ability (Table 3). Correlations ranged from 0.66 to 0.86. Most of these are highly significant, but the consistency of the sign and size of the correlations was the most remarkable feature of these results. The correlations among psychometric ability tests and the individual subtests of the Cambridge Mental Disorders of the Elderly Examination—cognitive section were computed. Of 66 correlations (i.e. 11 Cambridge Mental Disorders of the Elderly Examination—cognitive section subtests × Cattell Culture Fair Test of Intelligence, Form 2A and Digit Symbol Substitution Test × Alzheimer's, Korsakoff's and combined Alzheimer's/Korsakoff's groups, but note that the patients groups do not provide independent correlations), only four small, non-significant correlations were not in the expected direction. In the Alzheimer's group both Cattell Culture Fair Test of Intelligence, Form 2A and Digit Symbol Substitution Test correlated significantly with 5 of 11 Cambridge Mental Disorders of the Elderly Examination—cognitive section subtests,

TABLE 3. PEARSON (r) CORRELATIONS AMONG PSYCHOMETRIC AND CLINICAL TESTS OF COGNITIVE ABILITY IN ALZHEIMER AND KORSAKOFF PATIENTS, AND IN THE TWO GROUPS COMBINED (DECIMAL POINTS OMITTED FROM COEFFICIENTS.)

	Alzheimer		*Korsakoff*		*Alzheimer+Korsakoff*	
	CCF	*DSST*	*CCF*	*DSST*	*CCF*	*DSST*
MMSE	67	78	70	69	78	80
CAMDEX-Cog	66	80	68	83	78	86

CCF = Cattell Culture Fair Intelligence Test, Form 2A; DSST = Digit Symbol Substitution Test from the WAIS-R, CAMDEX-Cog = cognitive score from CAMDEX test; MMSE = Mini Mental State Examination.

while the numbers for the Korsakoff's group were 2 and 6, respectively. When the Korsakoff's and Alzheimer's groups were combined, the Cattell Culture Fair Test of Intelligence. Form 2A and the Digit Symbol Substitution Test each correlated significantly with 7 of the 11 Cambridge Mental Disorders of the Elderly Examination—cognitive section subtests. In general, the aspects of the Cambridge Mental Disorders of the Elderly Examination—cognitive section which showed the lowest correlations with Cattell Culture Fair Test of Intelligence, Form 2A and Digit Symbol Substitution Test were memory, abstraction and orientation. While proper caution must be urged in the interpretation of correlation coefficients based on a small number of subjects, the strong trend in the above results indicates that there is much shared variance in several Cambridge Mental Disorders of the Elderly Examination—cognitive section subtests.

DISCUSSION

In the present study, groups of subjects with pre-senile Alzheimer's disease, Korsakoff's syndrome control group were compared on a test of Inspection Time, which is an estimate of the speed of central visual processes. The groups were well balanced for age and pre-morbid intelligence, and were physically healthy and free from psychotropic medication. The results suggest that the Alzheimer's group was significantly impaired on this early stage of visual information processing when compared with both Korsakoff's and control groups. As a group, patients with Korsakoff's syndrome had a mean Inspection Time very similar to that of controls. This finding suggests that patients with Alzheimer's disease, but not patients with Korsakoff's syndrome, are deficient in one further information processing stage in addition to those discovered in studies such as Kopelman's (1985*a*,*b*).

The present study confirms other evidence that patients with Alzheimer's disease have relatively poor iconic processing (Miller, 1977; Schlotterer *et al.*, 1983). However, the present study overcomes two possible criticisms which may be made of earlier work. First, our groups were balanced for pre-morbid intelligence as well as age. This is necessary because, as will be clear from the present study, iconic memory processing indices are correlated with psychometric intelligence. Secondly, the adaptive staircase psychophysical procedure which we used provided, in effect, a reliability criterion for stopping subjects prior to assigning an Inspection Time to them. Schlotterer *et al.* (1983) used a method of ascending durations of stimulus persentation times, and the subject was stopped when four consecutive targets were named correctly (i.e. by indicating in each trial which of nine upper-case letters had been presented in a tachistoscope). This type of procedure is likely to punish those subjects who are less quick to pick up the rules of the test, and it involves a long period of chance-level responding before the longer stimulus durations are reached; this might be discouraging, particularly to subjects who are cognitively impaired. By contrast, the adaptive staircase begins with long durations and, after failures by the subject to identify the target correctly, will revert to easier discriminations. Further, it is sensitive to lapses of concentration during the session, and it will 'pull the subject back' to the start of the algorithm if they suddenly begin to respond less reliably than before, a phenomenon which we found especially with some of the patients with Alzheimer's disease. Miller's (1977) study used a different estimate from either the present study or that of Schlotterer *et al.* (1983). He estimated the mean number of letters (from an array of six) which could be reported by patients with Alzheimer's disease and age-matched controls when the letters were presented at durations ranging from 50 to 250 ms in a tachistoscope.

The finding that patients with Korsakoff's syndrome had similar Inspection Times to that of control subjects is at variance with the results of Oscar-Berman *et al.* (1973). They used a method of ascending limits in order to make threshold and critical stimulus interval determinations in a tachistoscopic task where briefly presented words and patterns had to be identified. Patients with Korsakoff's syndrome had elevated thresholds for stimulus recognition and increased critical stimulus intervals when compared with male alcoholic patients who did not suffer from Korsakoff's syndrome and with normal controls. However, they failed to balance the groups for age (the non-Korsakoff's alcoholic group was 9 yrs younger, and the normal control group was 25 yrs younger, than the Korsakoff's group), and premorbid intelligence was not estimated.

It has been widely recognized (Mackintosh, 1986; Vernon, 1986) that the Inspection Time/IQ correlation is probably higher in groups with impaired cognition. Until now this conclusion has been based on results from mentally handicapped patients. As far as we are aware, the present study is the first to measure Inspection Time and cognitive ability in patients with Alzheimer's disease and Korsakoff's syndrome. A particularly intriguing finding is that, despite a clear decline in cognitive functioning as assessed by the Cattell IQ and the Digit Symbol Substitution Test, the Korsakoff's group had a very similar mean and range of Inspection Times to the control subjects, and a similar association with pre-morbid IQ. Also, although the correlations were non-significant, the correlations between Inspection Time and other cognitive test scores in the Korsakoff's group were all in the expected direction. This suggests that the cognitive deficit in patients with Korsakoff's syndrome lies in processing capacities which are 'downstream' of those tapped by Inspection Time testing, but that Inspection Time remains rate-limiting.

Even within our small groups of subjects, the Inspection Time measure often correlated significantly with fluid-type intelligence estimates and with clinical tests of cognitive ability. When groups were combined to form a larger number of subjects the correlations were often greater than -0.6. One intepretation of this result is that a sizeable proportion of the variance in impaired cognition is explained by a slowing of central information processing speed, and that Inspection Time ability is tapped by such a large variety of mental tests that it appears to be a rate-limiting stage of cognitive processing. An alternative interpretation is that subjects with poorer cognitive ability have poorer 'attention' (Miller, 1977), or that they become bored with repetitive tasks, such as Inspection Time (Mackintosh, 1986). To some extent, the use of an adaptive psychological procedure can eliminate differences in task concentration, particularly intermittent lapses during a task. Also, Charman (1979) found that 'attentional set' made no difference to iconic memory performance in subjects whose age was similar to those tested here. Finally, Zhang *et al.* (1989*a*,*b*) have found that there are significant correlations between P200 indices of the average evoked potential when subject's evoked potentials are collected concurrently while they perform the Inspection Time task. They have hypothesized that the Inspection Time measure is related to stimulus discrimination processes. They failed to find correlations between Inspection Time performance and indices derived from pre-stimulus average evoked potentials (such as contingent negative variation) in the same conditions, which may have been expected if the Inspection Time was an index of attention to or general 'preparedness' for, the stimuli.

Inspection Time, Cattell Culture Fair Test of Intelligence, Form 2A and Digit Symbol Substitution Test all correlated significantly with the Mini Mental State Examination and the Cambridge Mental Disorders of the Elderly Examination—cognitive section and several of its subtests. Although the correlations were based on small numbers, this suggests that, although the Cambridge Mental Disorders of the Elderly Examination—cognitive section is divided into 11 subtests, there is much redundancy among them. One possibility raised by the present study is that the redundancy might be due largely to general intelligence, or Spearman's *g*. Therefore, a large-scale factor analysis study is required to validate the separation of the Cambridge Mental Disorders of the Elderly Examination—cognitive section items into the large number of subscales in the present form of the test.

In summary, Inspection Time is a psychophysical estimate which is an unambiguously measurable continuous variable. The discrimination involved is simple, but the resultant measure correlates with much more complicated cognitive tests. The stage of processing tested by the Inspection Time procedure (which is probably the efficiency with which information in iconic memory is transferred to discrimination processes) appears to be impaired in patients with pre-senile Alzheimer's disease, but not in patients with Korsakoff's syndrome, when compared with normal controls matched for age and pre-morbid intelligence.

REFERENCES

Brand CR, Deary IJ (1982) Intelligence and 'inspection time'. In: *A Model for Intelligence*. Edited by H. J. Eysenck. Berlin: Springer.

Cattell RB (1957) *Measuring Intelligence with the Culture Fair Tests: Manual for Scales 2 and 3.* Champaign, IL: Institute for Personality and Ability Testing.

Charman DK (1979) The ageing of iconic memory and attention *British Journal of Social and Clinical Psychology*, **18**, 257–259.

Crawford JR (1989) Estimation of premorbid intelligence: a review of recent developments. In: *Developments in Clinical and Experimental Neuropsychology*. Edited by J. R. Crawford and D. M. Parker. New York and London: Plenum Press, pp. 55–74.

Crawford JR, Stewart LE, Parker DM, Besson JAO, Cochrane RHB (1989) Estimation of premorbid intelligence: combining psychometric and demographic approaches improves predictive accuracy. *Personality and Individual Differences*, **10**, 793–796.

Deary IJ, Caryl PG, Egan V, Wight D (1989) Visual and auditory inspection time: their interrelationship and correlations with IQ in high ability subjects. *Personality and Individual Differences*, **10**, 525–533.

Folstein MF, Folstein SE, McHugh PR (1975) 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, **12**, 189–198.

Kopelman MD (1985*a*) Multiple memory deficits in Alzheimer-type dementia: implications for pharmacotherapy. *Psychological Medicine*, **15**, 527-541.

Kopelman MD (1985*b*) Rates of forgetting in Alzheimer-type dementia and Korsakoff's syndrome. *Neuropsychologia*, **23**, 623–638.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology, Cleveland*, **34**, 939–944.

Mackintosh NJ (1986) The biology of intelligence? *British Journal of Psychology*, **77**, 1–18.

Miller E (1977) A note on visual information processing in presenile dementia: a preliminary report. *British Journal of Social and Clinical Psychology*, **16**, 99–100.

Neisser U (1967) *Cognitive Psychology*. New York: Appleton-Century-Crofts.

Nelson HE, O'Connell A (1978) Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. *Cortex*, **14**, 234–244.

Nettelbeck T (1987) Inspection time and intelligence. In: *Speed of Information Processing and Intelligence*. Edited by P. A. Vernon. Norwood, NJ: Ablex.

Nettelbeck T, Hirons A, Wilson C (1984) Mental retardation, inspection time, and central attentional impairment. *American Journal of Mental Deficiency*, **89**, 91–98.

Nettelbeck T, McLean J (1984) Mental retardation and inspection time: a two-stage model for sensory registration and central processing. *American Journal of Mental Deficiency*, **89**, 83–90.

Oscar-Berman M, Goodglass H, Cherlow DG (1973) Perceptual laterality and iconic recognition of visual materials by Korsakoff patients and normal adults. *Journal of Comparative and Physiological Psychology*, **82**, 316–321.

Roth M, Tym E, Mountjoy CQ, Huppert FA, Hendrie H, Verma S *et al.* (1986) CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *British Journal of Psychiatry*, **149**, 698–709.

Schlotterer G, Moscovitch M, Crapper-McLachlan D (1983) Visual processing deficits as assessed by spatial frequency contrast sensitivity and backward masking in normal ageing and Alzheimer's disease. *Brain*, **107**, 309–325.

Sperling G (1967) Successive approximations to a model for short term memory. *Acta Psychologica, Amsterdam*, **27**, 285–292.

Taylor M, Creelman T (1967) PEST: efficient estimate on probability function. *Journal of the Acoustical Society of America*, **41**, 782–787.

Turvey MT (1973) On peripheral and central processes in vision: inferences from an information-processing analysis of masking with patterned stimuli. *Psychological Review*, **80**, 1–52.

Vernon PA (1986) Inspection time: does it measure intelligence? *Personality and Individual Differences*, **7**, 715–720.

Vickers D, Nettelbeck T, Willson RJ (1972) Perceptual indices of performance: the measurement of 'inspection time' and 'noise' in the visual system. *Perception*, **1**, 263–295.

Vickers D, Smith PL (1986) The rationale for the inspection time index. *Personality and Individual Differences*, **7**, 609–623.

Wechsler D (1981) *Manual for the Wechsler Adult Intelligence Scale–Revised.* New York: Psychological Corporation.

Zhang Y, Caryl PG, Deary IJ (1989*a*) Evoked potential correlates of inspection time. *Personality and Individual Differences*, **10**, 379–384.

Zhang Y, Caryl PG, Deary IJ (1989*b*) Evoked potentials, inspection time and intelligence. *Personality and Individual Differences*, **10**, 1079–1094.

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THE ROLE OF SENSORIMOTOR EXPERIENCE IN OBJECT RECOGNITION

A CASE OF MULTIMODAL AGNOSIA

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SUMMARY

Object recognition was studied in a 19-yr-old male patient who presented severe multimodal amnesia and agnosia without significant intellectual, linguistic or perceptual deficits. Bilateral temporal lobe lesions involved medial, polar and anterior infero-temporal structures. Although visual recognition was impaired to various extents for all categories of objects, preservation of certain capacities were demonstrated. In particular, the patient was able to determine specifically how to manipulate certain objects, in spite of his incapacity to define their function or their context of utilization. It is argued that object recognition involves different processing modes such that when direct access to representations of an object is impaired, sensorimotor information activated via alternative cortical and subcortical pathways may provide a limited mechanism for recognition.

INTRODUCTION

'You open on one side, stick something on it, close it, and it stays in. I can tell you how it works, but I don't see its exact use. I don't think I have seen one like this before, it is not a very common object.'

This is a response from a patient shown a *safety pin*. Although the first sentence might hint at a difficulty in naming, it is obvious from the subsequent statements that the object has not been recognized at all although it appears that the object is adequately perceived and furthermore, that some of its functional properties have been identified.

Associative agnosia, a deficit in object recognition in the presence of intact perceptual processing initially described by Lissauer (1890), offers an interesting opportunity to examine the neuropsychological aspects of object recognition. A growing number of case studies suggest that object recognition impairments may arise because of disturbances intervening at different points in a complex chain of processing events: from the extraction of the critical invariant features of objects (Riddoch and Humphreys, 1987*a*), to the *pre-semantic* categorization of visual information (Davidoff and Wilson, 1985), to accessing modality-specific (Warrington, 1975; Beauvois, 1982; Shallice, 1988) or supramodal (Ratcliff and Newcombe, 1982; Riddoch *et al.*, 1988) semantic storage and retrieval systems.

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In recent years there has been a growing interest in a form of agnosia resulting from dementia or most often from viral encephalitis causing extensive damage in the temporolimbic areas, and defined not only as a visual object recognition impairment but as a more general impairment in retrieving semantic information about objects from a variety of input modalities (e.g. Ratcliff and Newcombe, 1982; Warrington and Shallice, 1984). These patients may be unable to classify pictures of objects along specific dimensions, such as whether an object is used in the kitchen or whether an animal is dangerous (Warrington, 1975). They may fail to name an object, but also fail to draw it from memory given its name or verify the veracity of statements such as 'an oyster has four legs' (Sartori and Job, 1988). A major argument for the semantic nature of these impairments is the fact that certain categories of objects may be selectively affected while other categories appear preserved. Striking examples of such selective impairments are the agnosic patients reported by Warrington and Shallice (1984) and more recently by Silveri and Gainotti (1988) and Sartori and Job (1988). All of these reported cases showed a clear dissociation between their impaired ability to identify objects belonging to categories such as animals, fruits and vegetables and a preserved capacity to identify man-made objects such as tools or furniture.

Much discussion has recently taken place with regard to the underlying variables which are responsible for these selective impairments. One interpretation of the dissociation between the impaired recognition of *'living things'* and the normal recognition of *'man-made objects'* has stressed the distinction between sensory vs functional properties. As pointed out by Warrington and Shallice (1984), sensory properties may weigh more heavily in the identification of animals or foods while functional features may place a major role in the recognition of tools. These authors speculate that distinct semantic subsystems have evolved and become specialized for the processing of these two broad classes of attributes. Category-specific impairments would then arise as a result of the breakdown of one of these subsystems.

It may be pointed out that this account does not make explicit whether the organization proposed for the semantic system should be understood in terms of categories of *attributes* or categories of *objects*. Shallice (1988) reflecting on an earlier paper (Warrington and Shallice, 1984) argues that damage to the semantic system can be selective for a subsystem coding the sensory properties of objects while leaving intact the subsystem containing information about function. Warrington and McCarthy (1987) seem to suggest that while categories of object are built around specific attribute types, 'the end product of such processing is a categorically organized knowledge base' (p. 1290), by which we suppose the authors intend: organized in terms of *object* categories.

In a departure from these *semantic* interpretations, Sartori and Job (1988) explain category effects as an impairment at a pre-semantic level within a categorically organized system of structural descriptions of objects. Taking an even more radical stance, Humphreys and Riddoch (1988) argued that the apparent category-specific deficits in the cases reported by all of the above authors may be neither semantic nor category-specific. Since objects within categories such as animals, fruits or vegetables tend to resemble one another more than objects within the man-made category, selective disorders for the former categories could arise because of a 'noisy' transmission between the system that specifies structural attributes and the system that contains functional and associative knowledge. It is probably fair to say that although numerous arguments have been made in favour and against all of these proposals, the issue is far from settled. At stake are not only interpretations of clinical data but also models of semantic organization in terms of a unitary system of abstract representations vs multiple content-specific and/or format-specific subsystems, to use the terminology of Caramazza *et al.* (1990) who recently highlighted the lack of a clear neuropsychological theory of semantic organization that would allow testable predictions to be carried out.

In the following report we describe a pattern of object recognition impairments observed in a patient with medial and inferior temporal lobe lesions subsequent to viral encephalitis. Although recognition of all classes of objects was affected, a category-specific effect was found which honoured the man-made/living things distinction that has been reported in other similar cases, with relatively better recognition performances for tools than for animals and foods. Much of this report, however, focuses on the better preserved category, as we examined the kinds of attributes the patient could extract from visually presented objects. The main dissociation that we observed, and which is illustrated in the opening quotation of this paper, is that the patient was able to identify how to *manipulate* man-made objects while he could not recognize their *function*. That is, for the same object the patient could evoke both verbally and through gestures a specific pattern of action, but could identify no other semantic attributes such as its ultimate purpose or its context of use. Rather than postulating multiple selective impairments within a system of semantic representations, we argue that the pattern of within-category and across-category findings may be accounted for by a non-selective impairment, with a preserved capacity to identify certain attributes either through residual semantic mechanisms or via an alternative processing route, involving access to sensorimotor representations.

CASE REPORT

F.B. is a male engineering student and semi-professional musician who was hospitalized in May 1984, at the age of 19 yrs, for encephalitis of probable herpes origin. CT scan and MRI (Fig. 1) examinations recorded about 6 mths later, showed bilateral medial temporal lobe lesions involving hippocampal and amygdaloid structures as well as temporal neocortex bilaterally, and included the temporal pole and the most anterior part of infero-temporal cortex (Brodman's areas 38, 20 and 21). Neurological examination showed that all aspects of sensory and motor functions were strictly normal.

F.B. presented a set of neuropsychological disturbances dominated by recognition and memory impairments that he was at times painfully aware of, while intellectual, linguistic and perceptual functions were preserved. He recognized visually his parents but none of his friends or relatives, a deficit that has not cleared; he did not recognize personal objects as belonging to him; he was disoriented in his own house, his parents reporting that he often went to sleep in their bedroom thinking it was his. Most observers were struck by the puzzlement F.B. manifested in front of objects. He often behaved inappropriately with objects, mistaking shaving cream for toothpaste or vice versa, failing to find objects that he was asked to bring from the kitchen, or wearing clothes that were at odds with conventions or seasonal temperature. He was very confused with foods and was found eating a raw potato and frozen fish. His mother frequently observed him eating soup by first retrieving the noodles or pieces of vegetables with a fork, and using the spoon only for the broth. Neuropsychological testing was conducted in part during the patient's hospitalization and on an outpatient basis for a 1-yr period between July 1984 and June 1985.

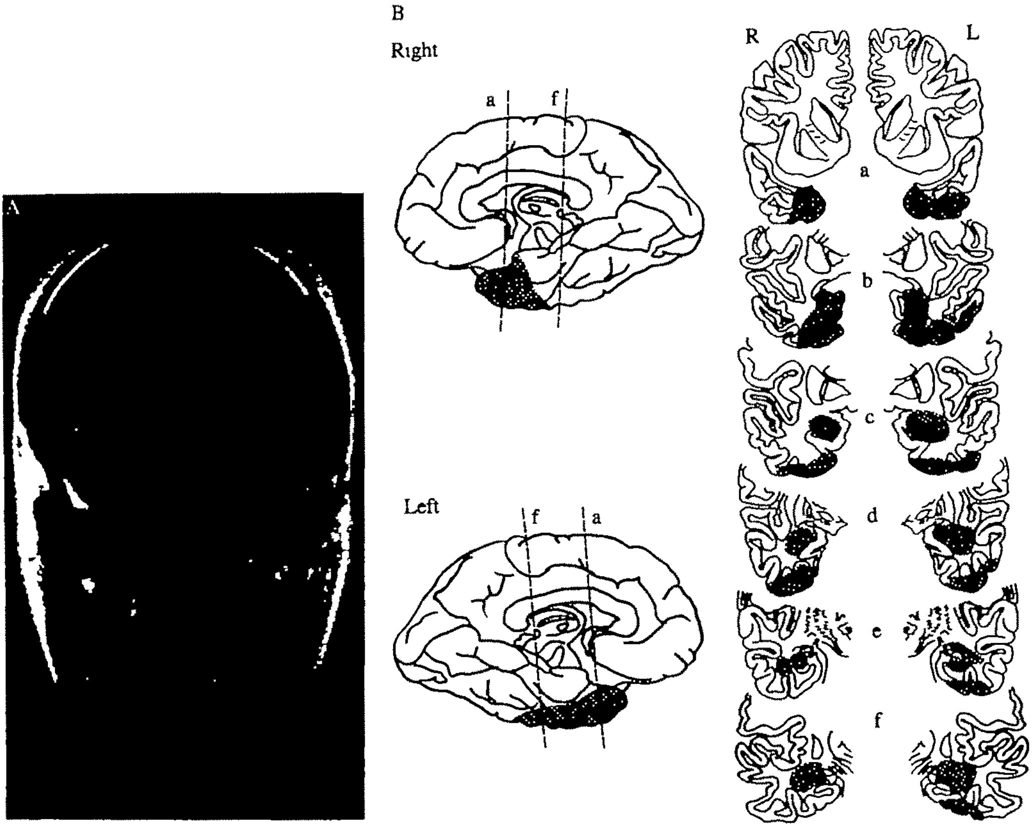

FIG. 1. A, representative coronal slice B, schematic reconstruction of MRI examination.

NEUROPSYCHOLOGICAL FINDINGS

Initial assessment (May 1984)

F.B. was densely amnesic for past as well as recent material. Although difficult to estimate with accuracy, the retrograde deficit covers almost all of the patient's lifespan and affects the recall of personal data, public events and personalities, and general didactic knowledge. Results on Signoret and Whitley's (1979) memory test (Batterie 144), showed poor learning capacities and no retention of visual or verbal materials (Table 1).

In spite of these difficulties, some learning capacities were manifested on repeated testing with Raven's progressive matrices (PM-38). Linear decreases were found in the time to complete the test (from 37 to 10 min) and in the number of errors (from 16 to 4) over five administrations of the test in a 24-h period, and this despite denial, at the beginning of each new administration, of ever having been shown the test. F.B. was also capable of learning new melodies on his guitar, a skill which according to his father, also a musician, has not been altered by the illness.

Full-scale, verbal and performance IQ scores obtained on the WAIS were in the normal range (102, 99, 105, respectively), though these scores certainly do not reflect the patient's premorbid functioning. It is noteworthy that the lowest results were obtained on the Information subtest, consistent with the memory impairment, while the Vocabulary and Comprehension scores were normal.

TABLE 1 IQ AND MEMORY TEST SCORES

WAIS age-scaled scores

Verbal IQ	99	Performance IQ	105
Information	4	Digit symbol	12
Comprehension	11	Picture completion	10
Arithmetic	8	Block design	12
Similarities	9	Picture arrangement	9
Digit span	13	Object assembly	11
Vocabulary	10		

Batterie 144 (Signoret and Whitley, 1979)

	FB	*Controls*
Visual+verbal average:		
Rote learning	23	58.7
Associative learning	39	66 7
Acquisition	22	66.5
Retention	1	65 3
Total verbal memory score	23	62.8
Total visual memory score	19.5	66

(Maximum score = 72)

Spontaneous speech was fluent and without paraphasias. Language profile on the French version of the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1972) was normal except for mild oral comprehension difficulties of isolated words which were reflected in a comprehension score of 5.5 (max. = 7). Reading comprehension was in keeping with oral comprehension. Some regularizing errors were also observed in oral reading and in writing to dictation.

Finally, there was no ideomotor, ideational or constructional apraxia.

Visual perception

Results on the following tests of visual perception and discrimination were strictly normal: visual acuity; visual fields; Farnsworth-Munsell 100-hue test of colour vision (Farnsworth, 1943); Thurstone's identical forms (Thurstone 1952); embedded figures (De Renzi and Spinnler, 1966); matching objects of the same shape but different sizes [an array of 10 pairs of identical objects (iron, key, coin, spool, spoon, scissors, cap, candle, pliers, pen), one member in a 'toy' size and the other member in its normal size, were visually presented to the patient who was asked to select those having the same shape]; matching pictures of objects presented from different perspectives [an array of 10 pairs of pictures of objects (baby's dummy, pencil-sharpener, lighter, telephone, ring, screwdriver, safety-pin, fork, match, light-bulb) were visually presented to the patient—one member of the pair was a canonical view and the other a non-canonical view of the object; the patient was requested to match the pictures representing the same object]; Benton's facial recognition test (Benton *et al.*, 1978).

Other tasks such as copying complex geometrical designs and pictures of real objects (line drawings but also coloured pictures with no line contours) were also well executed quickly and without the slavish, line by line copying strategy observed in many patients with apperceptive agnosia.

Visual recognition

As shown in Table 2, F.B. had difficulty in identifying objects and pictures of objects either verbally or by demonstration of use. A correct verbal response was defined as correct naming or description of use. A miming gesture describing the precise utilization of an object was considered a correct demonstration of use. F.B. also had difficulty in matching objects by pairs according to their associative characteristics (the patient was asked to match the objects that are usually found in the same place and/or that are used together). Correct descriptions of use were more frequent than correct naming. This indicates the presence of some word-finding difficulties, but the recognition performances were not improved by using strictly non-verbal responses (e.g. miming and matching tasks).

Recognition of other visual stimuli such as colours, faces and places were all severely impaired: colour

TABLE 2 VISUAL, AUDITORY AND TACTILE TESTS OF RECOGNITION

	Objects	*Drawings*
Visual object recognition		
Naming only	4/15	2/15
Naming or defining	6/15	5/15
Matching by function or by context	3/12	Not tested
Miming use	5/10	1/6
Tactile object recognition		
Naming or defining	6/10	
Miming use	5/10	
Auditory object recognition		
Naming or defining	8/20	
Miming use	11/15	
Sound–picture matching	12/20	
Other visual materials		
Colour naming	15/30	
Identifying appropriately coloured objects	4/12	
Colour–colour name matching	8/25	
Colouring object drawings	4/10	
Famous faces	0/15	
City landmarks	0/10	

Recognition of other visual stimuli such as colours, faces and places were all severely impaired: colour naming (15/30 correct); multiple choice identification of the appropriately coloured objects (4/12 correct); matching the names of objects with colour samples (8/25 correct) or pictures of objects with colour names (8/25 correct); colouring empty line drawings (4/10 correct). Some of these results may obviously be related to the deficit in object recognition. The patient failed to learn any new faces with repeated presentations of the same set of unfamiliar pictures, as would be expected from his anterograde memory impairment. Also none of 15 pictures of famous personalities and no pictures from a family album aside from those of his mother, father and himself were identified. He did not recognize any picture of city landmarks or famous buildings.

Tactile and auditory recognition

Identification of objects was also assessed by touch and from their familiar sound. All of 10 tactually presented objects were associated correctly with the identical stimuli presented visually. However, tactile identification by name or by gesture of use was impaired. Twenty tape-recorded familiar sounds were presented for identification by name, miming, sound-picture matching. As is shown in Table 2, performance was deficient in all tasks. Although familiar melodies were not identified by name, F.B. could play a complete melody on his instrument and sing some of the lyrics when cued by the first few notes.

Follow-up examination (July 1984–June 1985)

The previous section dealt with the pattern of impairments observed during F.B.'s initial hospitalization. The main purpose of presenting these data was to illustrate the multimodal character of the deficit (even though items were not exactly matched for all sensory modalities), and the fact that it extended over a broad range of stimuli. Although the memory difficulties did not improve significantly over time, some changes were observed in the object recognition performances during follow-up over a 2-yr period. Possible discrepancies between early and later performances on similar tests may be due to genuine changes or to the fact that we used different pools of stimuli. The following data represent a stable picture of F.B.'s preserved and impaired performances during this follow-up period.

Visual recognition of objects from different categories

In order to evaluate the possibility of a category effect on object recognition, we presented F.B. with pictures of tools, animals and foods, using three tasks largely inspired from the work of Warrington (Warrington, 1975; Warrington and Shallice, 1984) The pictures were presented in three conditions: (1) naming (10 items per category); (2) matching an auditorily presented name to a sample of four pictures from the same category (20 items); (3) classification according to a salient attribute of the category: for tools, used in kitchen, out of kitchen; for animals, living in France, out of France; for foods, sweet, not sweet (16 items per category).

F.B.'s performances are presented in Table 3 and show significant category effects in the naming (χ^2 = 7.08, $P < 0.05$), matching (χ^2 = 18.05, $P < 0.001$) and classification (χ^2 = 8.67, $P < 0.02$) tasks. The level of significance of the statistical test performed on naming performances should be interpreted cautiously due to the low number of correct responses. Better results were obtained for tools relative to the other two categories in the matching and classifications tasks ($P < 0.05$ or better) and for animals relative to foods in the matching task ($P < 0.01$). The rate of correct responses differed across tasks, indicating that task demands changed from one situation to another. Further probes of the patient's knowledge of the *hidden* visual characteristics of fruits ('does it contain one large or several small pits?') indicated that he was responding at the chance level. One exception to this pattern of poor performances with food items was when he explained correctly how to eat a banana.

TABLE 3. IDENTIFICATION OF TOOLS, ANIMALS AND FOODS

Test (no. of stimuli)	*Tools*	*Animals*	*Foods*
Naming (10)	5	2	0
Matching name (20) to sample	17	13	4
Classification (16)	16	11	9

Verbal recognition

Given our patient's marked difficulties in identifying objects from any sensory input, one may raise the question of his knowledge of objects as assessed from verbal input. Although in a previous task, F.B. classified man-made objects correctly on the basis of a single criterion (*see* Table 3), we had noticed that he did not perform as well with multiple criteria. In order to compare further visual and verbal recognition, we used a task in which either a picture of an object or its written name had to be matched to one of four classification criteria: belongs in the kitchen, in the living room, in the workshop, in the garden. He correctly classified 17/24 (71%) pictures and 23/24 (96%) corresponding written names, a marginally significant difference (χ^2 = 3.7, $P = 0.053$). This result suggests that verbal associations may be relatively better preserved than visual ones. Nevertheless, a certain number of other findings relative to object names are worth reporting here.

Concrete and abstract names. Speech samples on different imposed topics showed a contrast between elaborate and fluent statements made by the patient about abstract concepts, social values or feelings, and the poorness of his verbal productions on themes such as landscapes and seasons which showed a conspicuous absence of visual descriptors.

Results on the *letter-cued* word fluency test (60 s for each of the letters F, A, S) revealed that 29 of the 34 responses (82%) were abstract words. Three age-matched normal subjects that we have tested produced 42–60% abstract words in the same test.

In a *category-cued* word fluency test, F.B. gave 17 words for three object categories combined (60 s each for fruits, furniture, tools), while using abstract categories (feelings, occupations, countries) 37 words were produced.

In keeping with these results, definition of object names was adequate for 25/32 items, compared to 32/32 for abstract words equated for linguistic frequency (χ^2 = 5.77, $P < 0.02$). For example, F.B. defined *duck* as 'a small animal with four legs', *thimble* as: 'we often say sewing thimble' (Fr.: dé à coudre).

He could not say for which purpose a thimble is used, while he defined *society* as: 'a large group of people who live in the same manner and who share the same principles', and *culture* as: 'a way to learn life's customs, it varies from country to country'.

Naming from a description of functional vs sensory characteristics. Naming of various objects (including inanimate objects, animals and plants) from a definition was correct for 21/32 stimuli. However, the patient's score reached perfection when provided with three choices of semantically close alternatives. For instance, when asked, 'What is the animal that gives us milk?', F.B. did not evoke the name spontaneously, but recognized it immediately when given a choice between rabbit, cow and horse.

It must be noted that these definitions contained only functional or semantic descriptions of object attributes. In order to verify whether the performance in such a task is affected by the nature of the information supplied, we developed a test using two different kinds of definitions for the same set of target object names: verbal descriptions (1) of the function and (2) of the shape and physical characteristics of the objects. Silveri and Gainotti (1988) used a similar task, but with animals as stimuli.

Method. Four age-matched normal subjects and our patient were tested in this task. Two lists of verbal descriptions of common objects (pen, scissors, glove, television, fork, button, ladder, etc.) were constructed. The first list contained only descriptions of the object's function and the second list contained descriptions of the object's characteristic size, shape, materials. Two pilot subjects reviewed all of the descriptions and after eliminating those judged too ambiguous, two sets of 15 descriptions were selected. The two lists were presented orally, beginning with the visual descriptions. A ruler was placed in front of the subject in order to facilitate size estimation. The task was to name the target object, and if the subject failed, he or she was provided with a choice of three object names that included semantically- and morphologically-related distractors. Examples: 'a circular plastic disk, usually 1 cm or less in diameter with two or four holes in its middle' (visual); 'an object used to join the two sides of a blouse' (functional); 'a 10 cm by 20 cm object made of wool or leather, opened at one end and divided into five parts of various lengths at the other end' (visual); 'an object that wraps around the hand and which protects it from cold weather' (functional).

Results. The results shown in Table 4 indicate that normal subjects obtained perfect scores in both conditions. The numbers in parentheses indicate the correct responses given only after a choice of answers was given. All normal subjects were cued at least once by a choice of responses in the *visual descriptions* condition, indicating that this was somewhat more difficult than the *functional description* condition. A test of the difference between correct responses obtained in each condition excluding those obtained only from multiple choice, was significant ($t_{(3)} = 4.90$, $P < 0.02$).

TABLE 4 NAMING FROM VISUAL AND FUNCTIONAL DESCRIPTIONS BY NORMAL SUBJECTS AND PATIENT

	Visual description	*Functional description*
Controls		
S1	13 (+2)	15
S2	12 (+3)	15
S3	13 (+2)	15
S4	14 (+1)	15
F.B.	2 (+6)	12 (+2)

Numbers in parentheses refer to correct responses obtained after a choice of answers was provided.

F.B.'s performance was near perfection when tested with functional descriptions, but he was markedly impaired in the *visual descriptions* condition: only 2 of 15 target objects were spontaneously named and 6 more were identified with the aid of a choice of answers (the chance level would be approximately 4–5 correct choices). The difference between functional and physical descriptions was significant when computed on correct responses given without the aid of a cue ($\chi^2 = 10.85$, $P < 0.001$), and it remained significant even when cued responses were included in the analysis ($\chi^2 = 4.26$, $P < 0.05$). The magnitude of this difference is thus unlikely to be merely an effect of differential task difficulty.

Drawing from memory

Recall of the shape of objects can also be indirectly assessed in drawings of objects made from memory. Fig. 2 shows F.B.'s drawings on verbal command of (A) a guitar, (B) a fork, and (C) a hammer. With the exception of the guitar and despite being somewhat recognizable, the productions are quite poor when compared with the patient's graphic skills as assessed in copying tasks. Drawings from memory of fruits or animals were worse. All fruits looked like small circles, and all animals had the same generic four-legged animal shape, including the drawing of a hen. It is noteworthy that while the patient was drawing the guitar, he often paused and mimed the act of playing, as if the kinaesthetic cues helped him shape his representation. He acted in a similar way when drawing, adequately, a set of drums which is an instrument he also plays, but the drawings of all wind instruments, which he does not play, had the appearance of a stick.

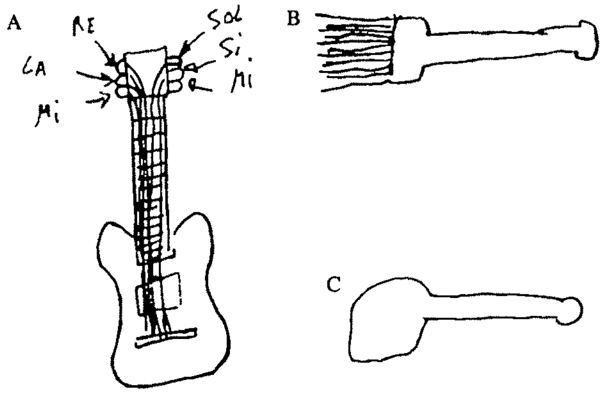

FIG 2. Drawing from memory on verbal command· (A) guitar, (B) fork and (C) hammer

Immediate recall of the shape is also impaired. Reproduction of abstract designs such as Rey's figure was failed. The immediate recall of pictures of objects showed interesting characteristics. Consider the example shown in Fig. 3. The patient was asked to copy a coloured picture (not a line drawing) of a watering can. The object was not recognized as such but F.B. tried to explain how it may work stating, 'some liquid is poured in through this opening', adding an arrow which is not on the original, and then, 'it comes out through that opening', adding the other arrow to indicate where this process takes place (Fig. 3A). After having spent a considerable amount of time discussing this object and having told him its name, the original and the copy were hidden and F.B. was asked immediately to reproduce the picture from memory. The result shown in Figure 3B is consistent with the two statements made about 'pouring in' and 'coming out', but the shape has vanished as he could not integrate those two functional features in a single drawing. Fig. 3C, D shows the drawings made from copy and immediate recall of a bagpipe, which the patient described as a liquid-containing object and never recognized as a musical instrument.

FURTHER INVESTIGATIONS

The remainder of this paper is mainly concerned with the preserved capacity of our patient to identify certain types of object attributes. Qualitative inspection of the data showed that although many of the patient's responses to visually presented objects were judged incorrect using standard criteria of success or failure,

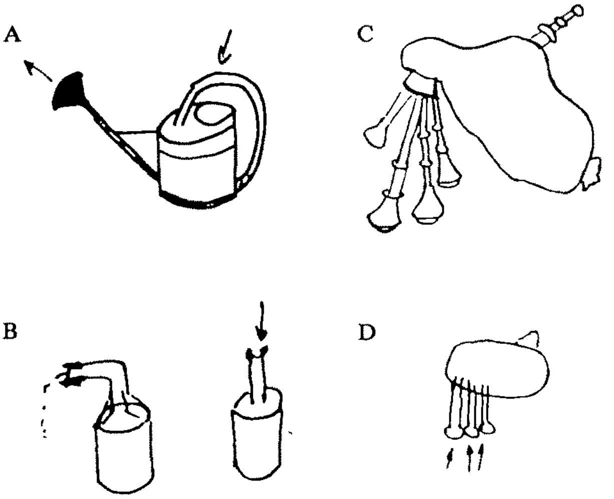

FIG 3. Drawings from a model and from memory (A) and (B) watering can, (C) and (D) bagpipe

certain properties of the stimuli appeared better identified than others. The following experiments were conducted in order to describe and analyse more precisely those capacities.

Identification of elementary physical attributes

The purpose of this task was to evaluate F.B.'s capacity to identify simple associative attributes that are unrelated to shape. We were interested in determining whether he could match actual information (mainly brightness and visual texture cues) to representations of non-visual properties of the same objects. Such an operation is involved for example when estimating visually the density or the weight of an object, presumably on the basis of previous cross-modal experience with objects. Although not necessarily critical, such cues can be important in fine categorization of objects that have similar shapes.

Method. Five attributes were examined: (*a*) texture; (*b*) temperature; (*c*) weight; (*d*) noise; (*e*) density. Stimuli were three different geometrical 3-D shapes (spheres, rings, and discs) made out of one of five different materials (wood, steel, foam rubber, cork, plastic). Each attribute was tested with two probe questions, one for each extreme along the relevant dimension· smoothest or roughest; warmest or coldest; lightest or heaviest; quietest or noisiest, softest or hardest. Three stimuli of identical shape but different materials were simultaneously presented and the patient was asked to point to the item which fitted the criterion (e.g. 'Which one would feel the heaviest? Which one is the softest? Which one would feel the coldest? the warmest?' etc.). Each question was asked four times (i.e. 8 trials per attribute) changing the composition of the stimulus array on every trial, for a total of 40 trials.

Results. Performance on this task was perfect with 40/40 correct responses for the five attributes. F.B. was able to anticipate correctly, on the sole basis of visual information, what he would feel in his hand if he could palpate the objects or what he would hear if he dropped them on the floor. The results suggest that F.B. can make multimodal associations from visual surface analysis, at least in a situation in which form is irrelevant.

Identification of anomalous objects

In order to assess further F.B.'s capacity to identify the attributes of certain objects, we presented him with pictures of objects transformed such as to make them functionally aberrant. Ten pictures of objects created by the artist Carelman (1984, Fig. 4), were intermixed with 10 pictures of real objects, and the patient was requested to simply determine whether each one existed or not. Riddoch and Humphreys (1987*b*) administered a similar task (using composite drawings made of parts of two different objects) as a test of visual access to structural representations of objects.

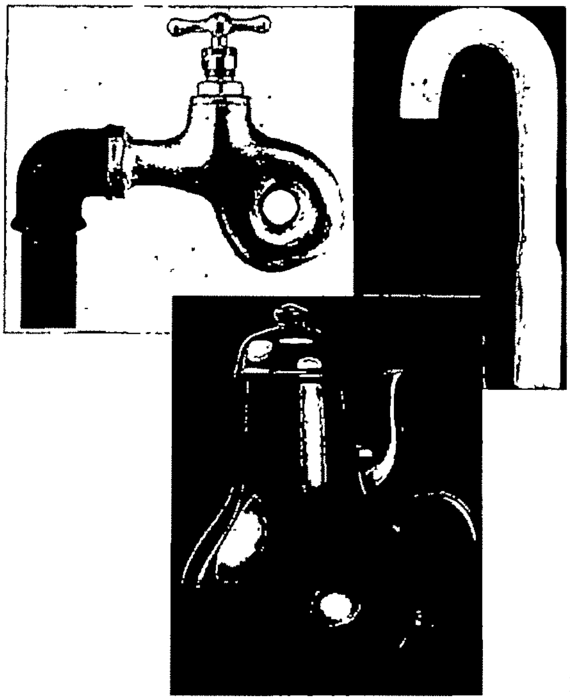

FIG. 4 Sample items of the anomalous objects test.

Results. All aberrant objects were correctly rejected without hesitation, and all real objects were classified as real. The patient justified spontaneously his decisions by stating where the anomalous feature lay, and indicated how the object should be redesigned in order to function. It is important to point out, however, that the anomalous features were usually identified in spite of evidence that the objects were clearly not recognized. For instance, as in the previously cited example of the watering can, F.B.'s description of the deformed coffee-pot contained the notions of 'liquid' and 'pouring', but he could not name it, give any detail as to the kind of liquid usually contained in it, the context in which it is used and for what purpose one may want to use it.

Should the perfect performance on this verification task be taken as an indication that access to structural information is preserved, and that whatever other object recognition impairment shown by F.B. must occur beyond this 'pre-semantic' stage, in terms of Riddoch and Humphreys' (1987*b*) model? This conclusion may not be warranted yet. In an attempt to examine further this issue, we subsequently presented four additional drawings of composite pseudo-objects that were *not* functionally incoherent. All four were wrongly classified as real, and F.B. proceeded to make up hypothetical utilizations, much as he did with unrecognized real objects. It does not appear then that object verification was achieved through a match between a percept and a stored prototype; instead as long as an object seemed to be functionally coherent, F.B. assumed that it was real. It may be that certain types of functional attributes of an object may be identified without complete access to all the structural information that is unique to this object. In the following section, we will introduce a distinction between the two kinds of 'functional' attributes, which may help to clarify the results obtained in this task.

Manipulation and function as two classes of object attributes: analysis of verbal and gestural responses

Many verbal responses of the patient were characterized by statements about the manipulation of objects on the one hand and their function or final purpose on the other. Gestures frequently accompanied or preceded these verbal statements. We were struck with the emphasis of the patient on the action one effects with an object and the accuracy with which it was described verbally, while at the same time such a statement was not always followed by an equally appropriate one about the finality of this action. In some cases, the object initially appeared to have been correctly identified but further probing indicated that it was not so. For example, when F.B. was shown the picture of a jackhammer, his immediate response was to mime the vibration while looking down on his hands placed in the appropriate holding posture, and said, 'It makes a lot of noise'. When asked what it was used for, he said, 'Probably to make holes . . .'. He paused and then added, 'in the wall . . . when you want to hang a picture'. In order to examine further the identification of *manipulation* and *function* of objects, we systematically reanalysed the patient's verbal responses and gestures to a new and larger sample of stimuli.

Method. Fifty common household objects were presented visually to the patient. He was not permitted to touch the stimuli. A subset of 20 responses were videotaped for the analysis of gestures. Manipulation was scored when a specific statement was made about how one manipulates the object ('hold this part in one hand', 'press here', etc.) or about an internal property of the object related to its manipulation ('it can be stretched with the fingers', 'if you rotate the top part, then you can pull it out'). Function was scored when the object was identified by a specific statement about the final use of the stimulus ('to erase mistakes on a sheet of paper', 'to pick up pieces of food from a plate'). Once tallied in this manner, these characteristics were then rated as appropriate or not to the object presented. For a subset of 20 videotaped responses, we rated in a similar way the frequency and adequacy of explicit spontaneous gestures describing the manipulation and function of these objects. Verbal responses were also evaluated for the presence of perseverations, semantic paraphasias, and confusions between objects of similar shape (*perceptual* errors).

Results. Adopting as criteria of successful identification either the name or a correct definition of function, 21/50 objects were recognized, which is consistent with our earlier observations (Table 5). The analysis of the responses for the remaining objects showed no instance of semantic paraphasia, extravagant response or perseveration. Ten out of 50 responses were descriptions of the function or manipulation of objects that resembled the stimulus but were clearly inappropriate (small pink candle: 'perhaps to spread colour on a piece of paper'), or consisted of a vague and irrelevant statement about a feature of the stimulus (electrical plug: 'something that you can stick into a hole and then twist'). Some responses contained the inappropriate concept but nevertheless included actions and functions that are *plausible* given the basic properties of the target objects. For example: *elastic band (decorative type, for hair)*: 'It looks stretchy [mimes the act of stretching something with both hands], it is probably some sort of ornament' [mimes the act of putting it around the wrist, like a bracelet]'; *plastic drinking straw (bent at its 'shoulder')*: 'Are there missing parts? Ah! You take it with something that contains water [makes a gesture evoking the shape of a container], to transfer water from one place to another [mimes the action of transferring something from a higher to a lower container], by aspiring it goes down like this [makes a gesture with a finger, showing the flow of water] . . . but its usefulness, I don't really see it.' (Compare this to the Webster definition of a siphon: 'a tube bent to form two legs of unequal length by which a liquid is transferred to a lower level'.)

The remaining 19 responses, however, contained description congruent with the specific manipulation of the target object even though the function was obviously not correctly identified. The following examples illustrate this quite clearly: *pliers*: 'It is used manually, when you pull apart here [points to handle] it opens up at the other end. Perhaps to hold several pieces of paper together'; *iron*: 'You hold it in one hand, and move it back and forth horizontally [mimes the action]. Maybe you can spread glue evenly with it'; *nail-clipper*: 'It can attach several sheets of paper together. You turn the piece on the top and tip it back [makes the precise finger movement sequence]. You press and it maintains them [mimes the action with thumb and index finger of the right hand while pointing to sheets of paper on the table with the left hand]'; *bicycle pump*: 'To take water [makes the gesture of holding the shaft with one hand and of pulling and pushing the handle with the other hand], you pull and then you eject it elsewhere'.

These results therefore indicate that appropriate statements were made about the manipulation of a large number of objects that were neither named nor recognized by function. Since F.B. did not describe the manipulation of all objects in the sample, a direct comparison of manipulation and function was done using only objects for which both attributes were described. F.B. was significantly more successful at telling how to use an object (19/23 83%) than what it is used for (5/23, 22% correct, McNemar's test, $\chi^2 = 12.07$, $P < 0.001$).

Explicit spontaneous gestures were present on 18/20 of the videotaped trials. Distinguishing *manipulation* from *function* in gestures can be difficult. In some cases, F.B. mimed precisely not only the action made on the object but also the context of its use. For example, in the case of the nail-clipper, he took a sheet of paper and made the gesture of using the object on one corner of the sheet. When it was not possible to determine unambiguously the identified function from miming, we used the score given for the corresponding verbal response. The identification of manipulation through gesture was correct for 14/18 (78%) of the objects, but only 5/18 (28%) of the same objects were identified by function (McNemar's test, $\chi^2 = 7.1$, $P < 0.01$).

TABLE 5 VERBAL AND GESTURAL RESPONSES TO VISUALLY PRESENTED OBJECTS

	Verbal responses (n = 50)
Function correct	21
Function incorrect, manipulation correct	19
Function and manipulation incorrect	10
	Gesture (n = 20)
Function and manipulation correct	5
Function incorrect, manipulation correct	9
Function and manipulation incorrect	6

DISCUSSION

The patient we have described presented with a complex amnesic and agnosic syndrome. In this study we opted to focus more particularly on his object recognition impairment. This was made possible at least in part by the remarkable preservation of general intellectual and linguistic abilities. A certain number of tentative conclusions can be drawn from our initial observations. First, it is quite clear that recognition of objects fails at a fairly high level of processing; secondly, *access* to representations of associative attributes of objects is severely impaired for most categories and from all sensory input modalities; thirdly, the results in the purely verbal tasks suggest that these representations themselves may be relatively intact. This latter statement must be qualified, however, since his spontaneous speech and word-generation performances contained few concrete words and object names, and since the patient was poor at retrieving shape information for purposes of naming from a physical description or drawing from memory. Difficulties in mental imagery, e.g. the process of conjuring up an internal visual representation from stored knowledge, and in immediate recall of shapes over brief intervals, may also compound the impairments observed in the latter two tasks.

These remarks suggest that the object recognition impairments observed in the present case may arise, to put it broadly, because the flow of information is interrupted at that stage at which various perceptual/structural and functional/associative object attributes must be mapped onto each other. Before further elaborating on the nature of impairment, let us review the major preserved capacities and discuss the nature of the mechanisms which can account for partial recognition of objects.

Preserved identification of object attributes

Preservation of certain *associative* capacities was demonstrated firstly with respect to elementary sensory or physical properties. In a task where visual surface but not shape cues are relevant, F.B. could determine the heaviness, the sound and the texture of various objects. Therefore aside from the obvious conclusion that the patient can accurately perceive visual textures, it is apparent that he can determine their significance as well. It is important to note that the task did not involve direct matching across sensory modalities. Instead, since only verbal instructions were used when the visual stimuli were presented ('which one is the heaviest?'), it probed the capacity to associate different visual textures with some form of representation of previous tactile and auditory experience. This finding obviously rules out an interpretation of the object recognition impairments as a global incapacity to form multimodal associations from vision. It also leads one to suggest that some *semantic* information can be extracted at a fairly early, shape-independent, processing of visual object attributes.

Associative capacities were also demonstrated at a level where shape characteristics must be taken into account. The patient was able to detect anomalies in the shape of various objects, especially when these anomalies rendered the objects functionally incoherent. This does not necessarily indicate intact access to representations of specific object prototypes, since the patient was liable to accept incorrectly as real, non-objects that were not functionally anomalous. However, it implies an intact capacity to identify the functional relevance of critical local features (a handle, a spout) as well as to identify the kind of spatial relationships those features must comply with for the object to achieve functional coherence.

The preserved capacity to identify such characteristics might account for the better recognition of tools than animals or food items. This possibility was in fact raised by Warrington and Shallice (1984) in order to account for a similar category effect in four post-encephalitic patients. These authors proposed that fine categorization may depend strongly on sensory attributes for natural kinds such as animals and plants, but less so for man-made objects which may be recognized primarily on the basis of their functional characteristics. More recently, Humphreys and Riddoch (1987) argued that there is a greater degree of perceptual overlap between members of natural than man-made categories. Impaired access to, or loss of 'structural' knowledge would therefore also be expected to create a recognition impairment more severe for the former than for the latter categories. Both views could account for other findings such as better naming from a functional definition than from a physical description, and the better preservation of functional than formal characteristics in drawing from memory (*see* Fig. 3).

Manipulation vs function of objects

It is important to stress that identifying a number of functional attributes does not necessarily permit the identification of an object's final use or purpose, which for most man-made objects is their absolute defining characteristic. The dissociation which emerged from the analysis of the patient's responses illustrates this point. By distinguishing statements about the manipulation from statements about the function of objects, we found that the patient could determine how to manipulate most objects and to a certain extent how they work, but could identify the function of less than half of these objects.

In optic aphasia, appropriate gestures can be made to visually-presented objects which are incorrectly named (Lhermitte and Beauvois, 1973). Riddoch and Humphreys (1987*b*) reported the case of a patient presenting this pattern of behaviour, but who also confused semantically close objects in matching and cued definition tasks which did not require explicit naming. Although these authors did not provide details about the gestures made for the items which were associated with semantic errors in the matching tasks, this observation raises the possibility that appropriate gestures may be made on the basis of initial feature extraction or stored shape information, even if semantic information about objects cannot be addressed. In the case of F.B., we provided evidence that the same objects which were not recognized, when using function and context of utilization as criteria, were identified correctly at the level of their manipulation. Although this can be inferred from gestural responses alone, verbal responses make an even more compelling case for this dissociation. In fact, the verbal report demonstrates that even if a specific and appropriate action pattern can be activated, it does not necessarily follow that other semantic information, even those semantic attributes that also relate to the object's function, has been accessed. Some responses (e.g. a jackhammer to make holes in a wall in order to hang a picture) as well as F.B.'s everyday behaviour bear witness to the fact that even if the object's function is apparently identified, some critical contextual information is still lacking. For instance, the sight of pieces of vegetables can activate the proper act of impaling them with a fork, even when these vegetables happen to be in the soup! Apparently, semantic knowledge about the *conventional* way of eating soup with a spoon regardless of whether it contains solid objects is no longer available to F.B.

What mechanisms make possible the extraction of such properties of objects, yet do not allow achievement of a more precise characterization in terms of their function or their context of utilization? One way to account for these results is to consider recognition as involving selective processes aimed at specifying an object's unique attributes or invariants. In this context, manipulation and general functioning of an object might be apprehended with a lower degree of selectivity than is required to identify its function. For instance, 'hand used', 'contains liquid', 'pouring' are redundant characteristics shared by different objects, but may not permit a distinction between a coffee-pot and a watering-can, both of which are handled in a similar manner but for clearly different purposes.

Could impaired visual categorization, because of loss of structural knowledge for instance (Humphreys and Riddoch, 1987), be expected to produce recognition failures of this sort? This hypothesis would predict a large number of errors characterized by wrong addressing of perceptually similar objects. Our patient did produce the response 'crayon' to the presentation of a small candle, both of which are coloured waxy cylinders, but such *perceptual* confusions were infrequent. Moreover, the patient was just as likely to misidentify the function of the target object by describing the function of an object that is clearly not visually similar ('to attach pieces of paper together' for *nail clipper*, 'to spread glue' for *iron*), or to simply describe an appropriate action or functional property of the object without giving any indication of having identified its unique function or having mistaken it for that of another object (namely, 'watering-can' example).

Another possibility is that the loss of selectivity is present in semantic processing *per se* as a result of impaired access to or partial loss of conceptual knowledge relative to this class of objects. Such a proposal would be in keeping with Warrington and Shallice's (1984) semantic memory impairment hypothesis. In their study, such impairments were said to be selective for certain *categories* since the authors claimed that recognition of man-made objects such as tools or furniture was totally preserved. In the present case, the semantic impairment can only be described as relatively selective as no one category was shown to be intact. Nevertheless, one could still explain the present results in terms of a semantic category hypothesis by suggesting that there can be quantitative differences in the degree of impairment among different object categories. Furthermore, there might exist, as Warrington and McCarthy (1987) proposed, finer-grained categorization in semantic memory which could have been overlooked in the present study. For instance, these authors observed a dissociation between impaired comprehension of small manipulable and preserved comprehension of large non-manipulable object names. However, it is difficult to imagine what finer categorization criterion could allow one to distinguish recognized from non-recognized items in the sample of 'small manipulable objects' which we used in this study.

Another possibility that we wish to propose and which might address more directly the manipulation/function dissociation is that 'how is it used?' and 'what is it?' are two qualitatively different questions that can be answered through distinct mechanisms.

Role of sensorimotor experience in object recognition

As stated previously a striking feature of F.B.'s verbal and gestural behaviour was his emphasis on the action performed on objects. This leads us to propose that the mechanisms mediating the preserved capacity to identify certain object attributes could involve sensorimotor experience. It is indeed through the act of palpating that one acquires the concepts of texture and density of objects. It is also through action upon objects that one learns about their functioning. We wish to use the term *sensorimotor* in a manner analogous to Piaget's (1967) who postulated that, during cognitive development, an initial identity exists between action and object, and action patterns are used to construct relationships, or make *constructional deductions* about the visual environment.

F.B.'s responses in object recognition tasks seemed to be guided by such a strategy. This was observed in his descriptions of several objects such as pliers ('when you pull apart the bottom pieces it opens up at the other end'), which reveal a precise analysis of their mechanical properties. Much gesturing accompanied these responses, as when the patient was shown an iron and he mimed a back and forth motion with his hand, assuming the exact posture for holding the iron by its handle. The presence of spontaneous gesture in this context might represent a self-cueing kinaesthetic strategy helping the patient to generate certain *hypotheses* about the function of objects. In fact, explicit gestures or covertly activated action patterns could be considered the main, if not the only accessible source of information about an object. To put it more strongly, it may be that in many cases semantic representations are not activated directly from vision, but indirectly through the representations of pattern of actions that a particular object specifically *affords*.

Such a mechanism would obviously reach its limits very quickly. It would do poorly at identifying the precise function and the proper context of use of objects. A semantic system reading the output of this sort of analysis might in fact propose that the function of back and forth horizontal motion is 'to spread glue evenly'. A frequent remark of the patient was, 'I can tell you how to use it but I have no idea what it is used for'. There were also frequent references to cutting, attaching, holding pieces of paper, perhaps because a stack of sheets on a desk was the only actual contextual cue in the laboratory situation. It would also do poorly for man-made objects that have few salient, well-differentiated functional features. Finally, it would do poorly at recognizing most living things, although it might be useful in recognizing certain food items that are manipuated in a unique fashion.

This hypothesis also suggests an alternative interpretation of the overall pattern of impaired and preserved recognition performances. Rather than postulating selective or categorical impairments within a domain of object representations, we would argue for the presence of a general recognition deficit, possibly due to access or storage impairments at the levels of unimodal (structural) and/or supramodal (semantic) object representations, the preserved recognition capacities being mediated by the visual activation of specific sensorimotor representations.

Structural implications

Lesions were found in several structures in the left and right anterior temporal lobes, including the medial temporal, polar and anterior infero-temporal regions. Although bilateral medial temporal lesions have long been known to be associated with severe anterograde amnesia, the functional role of the temporal poles is not well understood. These areas are defined as *paralimbic* on the basis of their cellular architecture (Mesulam, 1985), and connectional and physiological data do not indicate any relations with the 'ventral stream' visual association areas TEO and TE in the infero-temporal cortex (Ungerleider and Mishkin, 1982; Desimone and Ungerleider, 1989). Recent evidence in humans suggests that lesions of the temporal poles are associated with retrograde memory impairments (Eslinger and Cermak, 1988). Concomitant lesions of the internal and polar temporal regions could thus explain the severe retro-anterograde amnesia noted in the present case.

The lesions of the anterior portions of infero-temporal cortex may be more directly involved in the visual recognition impairments. The lack of evidence for any type of visual perceptual deficits suggests that these performances may be mediated by the more posterior areas. This is in agreement with studies in monkeys showing a functional gradient with greater effects of anterior infero-temporal (area TE) ablations on recognition and a greater effect of occipito-temporal ablations on discrimination (*see* Iwai and Mishkin, 1969). Positron emission tomography measures made during the performance of tasks known to be sensitive to area TE lesions in money, showed selective increases in regional blood flow in the occipito-temporal but not in anterior infero-temporal regions (Haxby *et al.*, 1988). This discrepancy between infero-temporal functional organization in monkeys and humans may indicate that the anterior infero-temporal cortex in man is devoted to a greater extent than in the monkey to high level processing of visual information and less to the perceptual analysis of shape, an idea consistent with the present data.

It has been proposed that visuo-motor and procedural learning capacities in amnesic patients can be mediated through a cortico-subcortical mechanism involving the neostriatum (Saint-Cyr *et al.*, 1988). We have shown in our patient the presence of preserved learning capacities with respect to guitar playing and visual-problem solving. It is interesting to speculate about the potential contribution of the cortico-striatal pathways in sensorimotor, action-based identification of functional attributes in object recognition tasks. The role of the basal ganglia in motor learning but also in certain cognitive activities such as procedural tasks, and their widespread connections with associative neocortex indeed suggests that such pathways could be involved in coding and in reactivating information generated through action.

Several regions in the posterior parietal cortex receive direct visual input from dorsal stream pre-striate areas. These areas contain neurons sensitive to visual parameters such as motion and orientation and play a role in integrating visual, somatosensory and motor information (Mountcastle *et al.*, 1975, Sakata *et al.*, 1989; Duhamel *et al.*, 1991). Such neural units may signal the presence of 'something' that can be acted upon in a certain way, although they may carry no other information about the objects themselves. Their visual messages could tell 'how to use it' but not 'what it is'.

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REFERENCES

Beauvois MF (1982) Optic aphasia: a process of interaction between vision and language. *Philosophical Transactions of the Royal Society of London,* B, **298,** 35–47.

Benton AL, Hamsher K, Varney RR, Spren O (1978) *Facial Recognition. Stimulus and Multiple Choice Pictures.* New York: Oxford University Press.

Caramazza A, Hillis AE, Rapp BC, Romani C (1990) The multiple semantics hypothesis: multiple confusions? *Cognitive Neuropsychology,* **7,** 161–189.

Carelman (1984) *Catalogue d'Objets Introuvables.* Poitiers: Balland.

Davidoff J, Wilson B (1985) A case of visual agnosia showing a disorder of pre-semantic visual classification. *Cortex,* **21,** 121–134.

De Renzi E, Spinnler H (1966) Visual recognition in patients with unilateral cerebral disease. *Journal of Nervous and Mental Disease,* **142,** 515–525.

Desimone R, Ungerleider LG (1989) Neural mechanisms of visual processing in monkeys. In· *Handbook of Neuropsychology,* Volume 2. Edited by F. Boller and J. Grafman. Amsterdam: Elsevier, pp. 267–299.

Duhamel JR, Colby CL, Goldberg ME (1991) Congruent representations of visual and somatosensory space in single neurons of monkey ventral intraparietal cortex (area VIP). In: *Brain and Space.* Edited by J. Paillard. Oxford: Oxford University Press.

Eslinger PJ, Cermak L (1988) Anatomic correlates of retrograde amnesia. *Society for Neuroscience Abstracts,* **14,** 1289.

Farnsworth D (1943) Farnsworth-Munsell 100-hue and dichotomous test for colour vision. *Journal of the Optical Society of America,* **33,** 568–578.

Goodglass H, Kaplan E (1972) *The Assessment of Aphasia and Related Disorders.* Philadelphia: Lea and Febiger

Haxby JV, Grady CL, Horwitz B, Schapiro MB, Carson RE, Ungerleider LG *et al.* (1988) Mapping two visual pathways in man with regional cerebral blood flow (rCBF) as measured by positron emission tomography (PET) and $H_2{}^{15}O$. *Society for Neuroscience Abstracts,* **14,** 750.

Humphreys GW, Riddoch MJ (1987) The fractionation of visual agnosia. In: *Visual Object Processing: A Cognitive Neuropsychological Approach.* Edited by G. W. Humphreys and M. J. Riddoch. Hove: Lawrence Erlbaum, pp. 281–306.

Humphreys GW, Riddoch MJ (1988) On the case for multiple semantic sytems: a reply to Shallice. *Cognitive Neuropsychology,* **5,** 143–150.

Iwai E, Mishkin M (1969) Further evidence on the locus of the visual area in the temporal lobe of the monkey. *Experimental Neurology,* **25,** 585–594.

LHERMITTE F, BEAUVOIS MF (1973) A visual–speech disconnexion syndrome: report of a case with optic aphasia, agnosic alexia and colour agnosia. *Brain*, **96**, 695–714.

LISSAUER H (1890) Ein Fall von Seelenblindheit nebst einem Beitrage zur Theorie derselben. *Archiv für Psychiatrie und Nervenkrankheiten*, **21**, 222–270.

MESULAM M-M (1985) *Principles of Behavioral Neurology*. Philadelphia: F. A. Davis.

MOUNTCASTLE VB, LYNCH JC, GEORGOPOULOS A, SAKATA H, ACUNA C (1975) Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *Journal of Neurophysiology*, **38**, 871–908.

PIAGET J (1967) *La Construction du Réel chez l'Enfant*. Neuchâtel. Delachaux et Niestlé.

RATCLIFF G, NEWCOMBE F (1982) Object recognition: some deductions from the clinical evidence. In: *Normality and Pathology in Cognitive Functions*. Edited by A. W. Ellis. London: Academic Press, pp. 147–171.

RIDDOCH MJ, HUMPHREYS GW (1987*a*) A case of integrative visual agnosia. *Brain*, **110**, 1431–1462.

RIDDOCH MJ, HUMPHREYS GW (1987*b*) Visual object processing in optic aphasia: a case of semantic access agnosia. *Cognitive Neuropsychology*, **4**, 131–185.

RIDDOCH MJ, HUMPHREYS GW, COLTHEART M, FUNNELL E (1988) Semantic systems or system? Neuropsychological evidence re-examined. *Cognitive Neuropsychology*, **5**, 3–25.

SAINT-CYR JA, TAYLOR AE, LANG AE (1988) Procedural learning and neostriatal dysfunction in man. *Brain*, **111**, 941–959.

SAKATA H, TAIRA M, MINE S, MURATA A (1989) Functional properties of the hand movement-related neurons in the parietal cortex of the monkey. *Proceedings of the First Annual Bristol-Myers Symposium on Neuroscience Research*, 49.

SARTORI G, JOB R (1988) The oyster with four legs: a neuropsychological study on the interaction of visual and semantic information. *Cognitive Neuropsychology*, **5**, 105–132.

SHALLICE T (1988) Specialisation within the semantic system. *Cognitive Neuropsychology*, **5**, 133–142.

SIGNORET JL, WHITLEY A (1979) A memory battery scale. *International Neuropsychological Bulletin*, **2**, 26–30.

SILVERI MC, GAINOTTI G (1988) Interaction between vision and language in category-specific semantic impairment. *Cognitive Neuropsychology*, **5**, 677–709.

THURSTONE LL (1952) *Test de Formes Identiques*. Paris: Editions Du Centre de Psychologie Appliquée.

UNGERLEIDER LG, MISHKIN M (1982) Two cortical visual systems. In: *Analysis of Visual Behavior*. Edited by D. J. Ingle, M. A Goodale and R. J. W. Mansfield. Cambridge· MIT Press, pp. 549–586.

WARRINGTON EK (1975) The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology*, **27**, 635–657.

WARRINGTON EK, SHALLICE T (1984) Category specific semantic impairments. *Brain*, **107**, 829–853.

WARRINGTON EK, MCCARTHY RA (1987) Categories of knowledge: further fractionations and an attempted integration. *Brain*, **110**, 1273–1296.

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COVERT AND OVERT RECOGNITION IN PROSOPAGNOSIA

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SUMMARY

Prosopagnosic patients suffer an inability to recognize familiar people by visual inspection of their faces. Despite the absence of overt recognition, though, some prosopagnosic patients continue to process the identities of familiar faces covertly. A longstanding controversy concerns whether the recognition deficit in prosopagnosia is specific for faces, or also affects other types of visual stimuli. We investigated whether the patient P.H , who has severe problems with within-class recognition of many types of visual stimuli, would show covert recognition for all stimuli which he cannot recognize overtly. Such a finding would be consistent with the idea that face recognition and recognition of other visually similar stimuli are performed by the same underlying functional mechanisms. We assessed this possibility with a forced-choice decision between correct and incorrect alternative names for familiar faces, cars and flowers, and with comparisons of P.H.'s ability to learn true versus untrue names to familiar faces, cars and flowers. Results indicated that P.H. does show covert recognition of cars and flowers, as well as faces. In addition, the covert effects observed in the forced-choice name decision and learning tasks used here were shown to have a potential common basis. Finally, the possibility of using covert knowledge as a basis for rehabilitation was explored. As was observed by Sergent and Poncet (1990) in their patient, P.H. could achieve some overt face recognition under very specific circumstances.

INTRODUCTION

The neurological condition prosopagnosia involves a selective impairment affecting the recognition of familiar faces. Typically, prosopagnosic patients are still able to perceive faces and identify the separate facial features. The identification of familiar people from other cues, such as the voice, remains intact, and recognition of everyday objects and words can be largely preserved (Bodamer, 1947; Meadows, 1974; Hay and Young, 1982).

On clinical testing, when presented with a photograph of a familiar face, a prosopagnosic patient will fail to name the person, to give any autobiographical information concerning that person, or even to realize whether the face is familiar or not. Bauer (1984) and Bauer and Verfaellie (1988) demonstrated that despite this absence of any *overt* sign of face recognition, prosopagnosic patients may continue to process the identities of familiar faces *covertly*. For example, Bauer (1984) showed the prosopagnosic patient, L.F., a series of photographs of familiar faces and presented

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auditorily 5 alternative names for each face. L.F. was at chance level in choosing the correct name when asked directly to do so. However, skin conductance responses occurred more often and with higher amplitude to the correct name than to the incorrect alternatives (*see also* Tranel and Damasio, 1985, 1988).

On the basis of this psychophysiological evidence, and careful analysis of the possible underlying anatomy and the particular lesion sites of his patient, Bauer (1984, 1986) suggested that an autonomic route to face recognition can be selectively preserved while the route to overt, conscious recognition is damaged.

Additional evidence for covert face recognition in prosopagnosia comes from the studies by Rizzo *et al.* (1987) who observed differential eye movement scanpaths for familiar and unfamiliar faces, and Renault *et al.* (1989) who recorded different P300 responses when their patient was looking at familiar compared with unfamiliar faces.

Other studies have explored the phenomenon of covert face recognition with a different set of paradigms, based more closely on techniques of experimental psychology. The first study was reported by Bruyer *et al.* (1983), who investigated a patient (Mr W.) with pronounced face recognition problems. They demonstrated that it was easier for Mr W. to learn correct than incorrect names to familiar faces which he found difficult to recognize.

In a series of studies with the prosopagnosic patient P.H. we confirmed that covert face recognition can be demonstrated using behavioural tasks (De Haan *et al.*, 1987*a,b*; Young and De Haan, 1988; Young *et al.*, 1988). The experiments developed to assess the presence and extent of covert face recognition for P.H. involved face matching, interference of distractor faces on name classification, associative priming of name recognition by face primes, and learning true and untrue items of information to faces. In all cases, the basic method involved the use of tasks which are sensitive to face identity but do not require the patient to make an overt face identification response. We will refer to these as tests in which face recognition is tested *indirectly*, in contrast to the more conventional *direct* tests of recognition (Young and De Haan, 1990, 1991). A direct task will immediately enquire about the ability of interest ('Whose face is this?', 'Which is familiar?', etc.), whereas in an indirect test the ability in question is introduced as an incidental feature of a task that ostensibly measures something else.

In many of these tasks the information which is accessed covertly is nonetheless dependent on precise visual discriminations, and must reflect the operation of sophisticated visual recognition mechanisms. For example, the results from associative priming tasks indicate covert processing of the identity of a face that has been presented quite briefly (Young *et al.*, 1988). Bauer's (1984) and Bauer and Verfaellie's (1988) Galvanic Skin Response results also involved covert processing of identity, and so did Sergent and Poncet's (1990) finding of preserved ability to match photographs of the same person's face across a 30-yr age difference (using photographs of the people taken in 1955 and 1985). By 'processing of identity' we mean that the visual system can narrow down the possibilities to the face of a specific person from all the thousands it has encountered in the past, and that it is still capable of using this information in certain ways (as reflected in Galvanic Skin Response changes, associative priming, interference, etc.). We do not seek to claim that this means there is also covert retrieval of any very detailed semantic information about the individual (Young and De Haan, 1988).

De Haan *et al.* (1987*b*) suggested that covert face recognition effects were derived from the mechanisms which underlie normal overt recognition. These mechanisms have been relatively preserved, but the patient cannot achieve overt access to this information. This would, for instance, be the case if a brain injury damages the outputs of otherwise intact face recognition units (Young and De Haan, 1988). A similar proposal has been made by Sergent and Poncet (1990), who also used the learning paradigm to show covert face recognition in a prosopagnosic patient. These accounts of covert recognition in terms of preservation of part of the mechanism responsible for overt recognition are not necessarily inconsistent with Bauer's (1984, 1986) dual route explanation (which hypothesizes that processes involved in overt recognition are damaged while the autonomic route is preserved) if it is accepted that the two routes diverge *after* perceptual classification of the face has been achieved.

Although both psychophysiological and experimental techniques have produced findings of covert recognition, it is important to note that not all prosopagnosic patients show covert recognition. Bauer (1986), Newcombe *et al.* (1989), Sergent and Villemure (1989) and Young and Ellis (1989) have all described cases in which *both* overt and covert face recognition are lost. Hence, it is now becoming clear that covert face recognition tasks can provide a means to differentiate between patients who are otherwise comparable on direct recognition tests.

The present studies were aimed at further exploration of covert recognition in the patient P.H. (De Haan *et al.*, 1987*a,b*; Young and De Haan, 1988; Young *et al.*, 1988). Our starting-point concerned the question whether P.H.'s covert visual recognition was restricted to face stimuli, or whether it was a general feature of his recognition impairment. P.H.'s ability to identify exemplars from categories with many visually similar items was very poor. This problem of 'within-class' recognition is a common observation in prosopagnosia, and some researchers have claimed that it is the crucial deficit (Duensing, 1952; Damasio *et al.*, 1982; but *see* De Renzi, 1986). It thus becomes intriguing whether P.H., who showed such clear effects of covert recognition of familiar faces, would demonstrate similar effects with other classes of objects whose exemplars he could not recognize overtly. Findings of covert recognition of other stimulus classes than faces would be consistent with the idea that a common deficit is involved, whereas findings of covert recognition for faces only would invalidate this view.

Further work with P.H. was also instigated by the findings of Sergent and Poncet (1990) who employed, among others, a forced-choice name decision task to demonstrate covert face recognition. A series of photographs of famous faces was presented, with two alternative names for each item (the name of the owner of the face and a foil). Sergent and Poncet's (1990) patient, P.V., was above-chance in choosing the correct name, although she maintained she was guessing. This subjective report was confirmed by subsequently presenting the faces with two invalid names (i.e. neither of the names belonged to the owner of the face). P.V. continued choosing one of the names, without realizing this deceit. Had she performed the original test on the basis of some rudimentary overt knowledge, then she should have noticed the absence of a correct response in the alternatives given to her.

Our interest in this finding is that the task seemed to elicit covert knowledge even though it was a direct recognition test (since the patient was asked directly which was the correct name). We wanted to know whether this would also hold for P.H., whose performance of other forced-choice tasks (such as choosing which of two faces is familiar) had been at chance level (Young and De Haan, 1988). In addition, we wanted to investigate the possible confounding effects of preserved face imagery. If the patient could still construct mental images of the two named people, then he/she could compare these mental images with the presented face photograph and select the correct name on the basis of the best match. A further question concerns the relation between the covert recognition effects elicited by Sergent and Poncet's (1990) forced-choice name decision task and the learning of true and untrue face-name pairings. We were able to show that these have a potential common basis.

An important observation in the Sergent and Poncet (1990) study was that overt recognition of famous faces could be provoked under certain experimental conditions. They showed P.V. 8 politicians' faces, for identification. As expected, she was unable to do so, but when the authors commented that they all had the same occupation, P.V. correctly inferred that they were politicians. Subsequently, she started to recognize the faces overtly, and without prompting named 7 of the 8 faces. The same phenomenon was observed with another semantic category (actors), but two further categories (singers and television personalities) failed to elicit any overt recognition. For these latter two categories P.V. was unable to produce the occupation spontaneously, and when the experimenter told her the occupational category she still did not recognize any of the faces overtly. When the faces of politicians and actors who had been recognized during the category presentation were presented again, but interleaved with celebrities from the other categories, P.V. failed to recognize any of them. Thus, overt recognition only happened under particular experimental conditions, and did not persist when these were changed.

In short, this method of 'category presentation' has been shown to provoke overt recognition in prosopagnosia, provided the patient can spontaneously determine the category. Given the important implications for theory and rehabilitation, we investigated the possibility of provoking overt face recognition in P.H. using two different procedures; one derived from Sergent and Poncet's (1990) work, and one from considering P.H.'s deficit as a possible form of semantic access impairment (Warrington and Shallice, 1979; Shallice, 1987).

CASE DESCRIPTION

In 1982, at the age of 19 yrs, P.H. was involved in a road traffic accident in which he sustained a severe closed head injury. The physical, ophthalmological, and neuropsychological sequelae have been described in detail by De Haan *et al.* (1987*b*), and only the essential points will be reiterated here. On examination in 1985 his intellectual abilities were reduced on the performance subtests, but in the average range on the verbal subtests of the Revised Wechsler Adult Intelligence Scale. Language functions were relatively preserved, and he could read without difficulty. P.H.'s short-term memory was intact with verbal and visual material, but long-term memory was severely reduced in both domains. He was unable to recall any items from two short paragraphs of prose (Wechsler memory scale) read to him an hour earlier, and his delayed (45 min) reproduction of the complex Rey-Osterrieth line drawing was very meagre. It was noted that this pronounced anterograde memory deficit on formal tests was not generally reflected in his everyday life. He was well oriented and could give a coherent account of his daily activities.

P.H. had a variety of problems in visual and spatial perception. For instance, contrast sensitivity for the middle and high spatial frequencies was reduced, and he had problems perceiving the three-dimensional structure in a line drawing of a block model in order to count the number of blocks that touch a particular block. In contrast, he could read very small print, and had no colour perception problems.

Faces were recognized as such, and easily distinguished from animal faces. However, matching of photographs of unfamiliar faces (Benton and Van Allen, 1973), recognition of emotional facial expressions, and race and gender discriminations were all at least moderately impaired. Overt recognition of familiar faces was nearly always unsuccessful, but people whose faces remained unidentified were easily recognized from the name or the voice.

P.H.'s visual recognition problems were not confined to faces. Other types of within-class recognition (Damasio *et al.*, 1982), such as for cars or flowers, were very poor, and on object-naming tasks he would demonstrate a mild degree of object agnosia.

The extent of P.H.'s face recognition problems on direct tests is most striking. During the last 5 yrs that we have been working with him, he has only occasionally recognized a face overtly. For example, he has begun to recognize Margaret Thatcher fairly consistently, sometimes Ronnie Corbett or Roger Moore, and once one of the authors, but even so he has failed to recognize all these people on other occasions. There are around a dozen faces that have occasionally been recognized in this way. These exceptions are noteworthy because his inability to recognize faces overtly is so severe. Given that quite a few of our photographs of familiar faces have now been shown to P.H. many times, though, it might be considered that he may be remembering some of the particular photographs. We certainly think this possible for people like Ronnie Corbett and Roger Moore, who are often not recognized (and were never recognized when we first started working with P.H.), but Margaret Thatcher has been recognized by P.H. from quite a few different photographs. This tiny fragment of evidence suggests that his overt recognition impairment may not be completely insuperable; a point we will return to later.

A recent MRI scan shows bilateral abnormal signal in the temporo-occipital junction, mainly in the inferior surface.

TESTS, RESULTS AND DISCUSSIONS

Within-class recognition

Previous studies with P.H. were focused on the presence and extent of his covert face recognition abilities (e.g. De Haan *et al.*, 1987*a,b*; Young and De Haan, 1988; Young *et al.*, 1988). The aims of the present investigation were to study his other within-class visual recognition difficulties in the context of covert processing, and to investigate whether overt face recognition could be provoked by different procedures.

Forced-choice name decision

We began by using Sergent and Poncet's (1990) forced-choice name decision task with P.H. In this task, two alternative names are given for each face, and the patient is asked to choose between them. We were interested to see whether the task would elicit P.H.'s covert knowledge, since it is a direct recognition test, and P.H.'s performance of other direct tests (including forced-choice familiarity decisions) has been at chance level (De Haan *et al.*, 1987*b*; Young and De Haan, 1988).

Like Sergent and Poncet (1990), we also employed presentation of faces with two untrue names to explore P.H.'s insight into his performance. As a further test of this, confidence ratings were taken.

Procedure. The task was divided into 4 stages. The first stage (standard) involved 40 black and white photographs of faces of media celebrities, presented one at a time. Two alternative spoken names were given for each face; one was the correct name, and the other was the name of another celebrity with the same occupational background. For example, the face of John Kennedy might be presented with the alternatives 'John Kennedy or Jimmy Carter'. P.H. was asked to select the correct name, and to rate his confidence in his choice on a 1–5 scale (1 = 'guess', 5 = 'certain').

In the second run of the test (incorrect face), the face photographs were changed to those of other celebrities so that now both names were untrue, i.e. neither of the name alternatives corresponded to the identity of the face. The new faces belonged to people with a similar occupation to the owners of the original faces. P.H. was not informed about the nature of this change, and was again asked to select the correct name and estimate his confidence in the response.

The next condition (incorrect name) also involved two untrue names, but now the original (standard) procedure was adapted by replacing the true name with the name of another celebrity with the same occupational background. P.H. was asked to select the correct name and estimate his confidence in the response.

Finally, the original (standard) test was repeated, to make sure that any changes in confidence ratings were not simply due to repetition of tests.

Results. The first observation from Table 1, where the results on this task are summarized, is that although P.H. was by no means very good at this task, his performance of the standard condition was above-chance (first administration: 27/40 correct, z = 2.06, one-tailed $P = 0.02$; retest: 26/40 correct, z = 1.74, one-tailed $P = 0.04$). There was, of course, no score for the two conditions with two incorrect alternatives.

P.H.'s confidence ratings were very low in all conditions, and he considered the majority of his responses to be complete guesses. More importantly, there was no difference between the conditions with a possible correct answer and those where both name alternatives were incorrect. The number of items on which P.H. rated his confidence higher than 1 (i.e. more confident than a complete guess) was 13/40 and 16/40 in the standard conditions, and 16/40 in the incorrect face and 14/40 in the incorrect names conditions.

TABLE 1 FORCED-CHOICE NAME DECISION WITH CONFIDENCE RATINGS (ON A SCALE FROM 1 TO 5) TO FAMILIAR FACES IN DIFFERENT CONDITIONS

			Confidence ratings	
Order	*Condition*	*Correct*	*Mean*	*SD*
1	Standard	27/40	1.43	0.71
2	Incorrect face	–	1 53	0.82
3	Incorrect name	–	1.53	0.85
4	Standard (retest)	26/40	1.60	0.87

Standard = 40 faces, each with one true and one untrue name alternative, incorrect face = same names as in standard, but with different faces so that both name alternatives are incorrect, incorrect name = same faces as in standard, but with two incorrect name alternatives

Discussion. When presented with a photograph of the face of a familiar person and two possible names, one of which was the name of the owner of the face, P.H. could select the appropriate name with above-chance accuracy. When asked how he performed this task, he consistently reported that he was 'guessing', and did not experience any confidence in his decisions. These subjective comments were substantiated by the fact that often when he had selected the incorrect name his response was judged to be more than a guess, and there was no difference in mean confidence ratings, or in the absolute number of items which were classified as complete guesses, between the conditions which did include a possible correct answer and those in which neither of the name alternatives was valid. Taken together, the incorrect face and incorrect name conditions involved 80 trials in which the correct name was not present, yet P.H. never expressed any hint that he thought that neither name was correct, or that any deception was taking place. The fact that P.H. was completely oblivious to this experimental manipulation strongly indicates that he was indeed guessing, without any sense of overt recognition of the correct face-name combinations.

These findings replicate those of Sergent and Poncet (1990) with P.V. However, because the procedure involves giving names, we were aware of the possibility that P.H. might try to construct an internal image of the two named people and subsequently match these images against the presented face photograph. Although he denied doing this, it was considered useful to make a formal test of his ability to image faces.

Face imagery

On a number of occasions the matter of seeing the face of someone 'in the mind's eye' was discussed with P.H. He clearly understood the concept, and he was adamant that he had lost this ability. As he put it, 'I can't get a picture'. Even when he was queried about the appearance of celebrities with particularly striking facial features (e.g. Denis Healey, a British politician with prominent eyebrows), P.H. would maintain that he no longer had any idea what they looked like. Only once did he make any other comment in this context; this concerned Margaret Thatcher, and was apparently instigated by his opinion of her rather than the way she looks. In addition, he had no image of personally familiar people, being unable to give even a remotely adequate description of members of the department where he has been seen regularly for the last 5 yrs.

Research into mental imagery is notoriously difficult, because it is often hard to determine whether responses are actually based on imagery or whether other sources of information such as semantic information have been used (e.g. Farah *et al.*, 1988). The method developed here specifically addresses *face* imagery, and the hypothesis is that a patient who has lost this ability should fail completely on the task.

Procedure. The test consisted of 20 trials, each involving 3 names of famous people. These people were chosen by the authors so that 2 were of similar appearance and 1 dissimilar. On each trial, subjects were instructed to image the faces of all 3 celebrities, and to decide which looked most alike This question was given in a 2-choice format. For instance, 'Who looks more like Elizabeth Taylor; Joan Collins or Barbara Windsor?' There was no time limit.

Results. Nine normal people of comparable age to P.H. were used as control subjects on this face imagery task. Of course, correct performance is defined simply as agreement with our own opinion of similarity in each case. The results are presented in Table 2, and it is clear that P.H. is not only severely impaired on this task in comparison with the normal subjects, but he performs no better than chance level.

TABLE 2 NUMBER CORRECT (MAX = 20, CHANCE = 10) ON THE FACE IMAGERY TASK FOR P H. AND 9 AGE-MATCHED CONTROL SUBJECTS

P.H.	10
Control subjects. mean	17.00
SD	1 60

Discussion. This experiment has confirmed the anecdotal evidence that P.H. is unable to construct a mental image of familiar faces. This is not an unusual finding (e.g. Bruyer *et al.*, 1983; Levine *et al.*, 1985; Habib, 1986), although some reports have described intact face imagery in prosopagnosic patients (e.g. Assal *et al.*, 1984) The main implication of this observation here is that it contradicts any suggestion that P.H. might be able to use face imagery to perform above-chance on the forced-choice name decision task.

In the experiments presented thus far we have eliminated two explanations of P.H.'s impaired but above-chance performance on forced-choice name decision. He could not have been using face imagery, and he was not using some form of overt recognition of the true face-name pairings. Therefore, we agree with Sergent and Poncet's (1990) conclusion that this task can register covert recognition of familiar faces.

Forced-choice name decision with faces, flowers and cars

P.H. has no difficulty in the visual recognition of most common objects, but he does have severe problems with identifying exemplars of categories with many visually similar items, such as cars or flowers (cars: 3/33; flowers: 0/26; De Haan *et al.*, 1987*b*). This impairment offers the possibility of addressing the question whether P.H.'s covert recognition is restricted to familiar faces, or whether it is present for all visual stimuli which he cannot recognize overtly.

Since we concluded that the forced-choice name decision task can register covert recognition of familiar faces, it was obvious to see if this extended to cars and flowers. Hence we investigated above-chance name decision with one true and one untrue name to photographs of familiar faces, cars and flowers.

Procedure. This task involved black-and-white photographs drawn from 3 different stimulus classes. There were 40 photographs of famous faces (from the standard task, described above), 44 photographs of prominent models of well-known makes of cars, and 26 photographs of widely grown garden flowers.

The faces, car and flower tests were administered in separate blocks. Each stimulus was presented individually with 2, orally stated, alternative names (1 correct, 1 incorrect). P.H. was asked to choose the name he thought belonged to that particular stimulus, and if he was unsure to guess. The incorrect name alternative was for the faces the name of another celebrity of the same sex with the same occupational background, for the cars a different car with similar characteristics (sports car, hatchback, etc.), and for the flowers the name of a similar type of plant. The order of presentation of the correct and incorrect name was varied in a pseudo-random order. These tasks were given on 4 different occasions, spread over more than 2 yrs, with at least 1 mth interval between sessions.

Results. Overt identification of the stimuli was virtually impossible for P.H. On occasion he would correctly name a picture, but this response was always based on some particular characteristic. For instance, in some of the photographs of cars part of the name or emblem of the make was just visible. During subsequent sessions these items were often not correctly recognized.

On the forced-choice name decision tests, P.H. continually claimed to be guessing. His performance (in terms of percent correct choices) of each test on 4 separate occasions is summarized in Table 3. It is clear that although he was still very impaired using this response procedure, his performance indicates some degree of recognition for each of the 3 types of stimuli. This pattern is especially consistent with the faces, but also apparent on the flowers and the cars, especially in his overall level of performance.

TABLE 3 P.H.'s PERFORMANCE IN PERCENTAGE CORRECT ON FORCED-CHOICE NAME DECISION WITH FAMILIAR FACES, CARS AND FLOWERS ON 4 SUCCESSIVE OCCASIONS

	Session				*Overall*	
	1	*2*	*3*	*4*	*Mean*	*SD*
Faces	75	68	65	68	69	3.7
Cars	53	71	62	59	61	6.5
Flowers	54	81	62	62	65	9 9

Discussion. Although he was unable to identify reliably any of the photographs overtly, P.H. performed at above-chance levels on these forced-choice name decision tasks. In the previous sections we confirmed that this pattern of performance can arise from covert processing. It is thus particularly interesting that above-chance performance was found for stimuli from all 3 classes. This suggests that P.H.'s covert identification is not restricted to faces, but actually involves other types of stimuli which pose recognition problems.

In order to establish the phenomenon of covert within-class discrimination more firmly, we used a different experimental paradigm; learning of true and untrue picture-name associations

Learning of true and untrue picture-name associations

In this experiment we investigated the possibility of covert recognition of visually similar stimuli, such as cars and flowers, using the learning paradigm developed by Bruyer *et al.* (1983) and De Haan *et al.* (1987*b*).

Procedure. Again, 3 classes of stimuli were used: familiar faces, cars and flowers. The general procedure followed that used by De Haan *et al.* (1987*b*, Task 7) Items were only considered for inclusion in the learning tasks for which P.H. had chosen the wrong name in a forced-choice name decision test which used the standard procedure described in the previous section. Six such items in each stimulus class (faces, cars or flowers) were allocated to either the true or the untrue condition, in such a way that the items within each condition were similar in general appearance The 3 items in the true condition retained their own name, whilst in the untrue conditions the names of the 3 items were interchanged.

The test procedures were identical in all 3 tasks (i.e. with faces, cars or flowers as stimuli). The 6 photographs were spread out before P.H. on the table in a random 2×3 matrix, and he was twice instructed as to which name was to be associated with each picture. The test involved 12 trials, each begun by reshuffling the photographs. Then P.H. was asked to point to the photograph corresponding to a name that was stated orally. If he made a mistake, he was corrected. All 6 names were presented in a different random order on each trial.

Results. Data consisted of the number of correct choices of the stimulus to go with true or untrue names on each trial. The statistical procedure followed the method used by De Haan *et al.* (1987*b*). The difference between the two conditions (true versus untrue name) was analysed with the sign test. Each of the 12 trials involved 6 responses, and the number of times P.H. pointed to the correct photograph was counted separately for each trial (max = 3) for the true and untrue pairings Raw scores are presented in Table 4.

Each trial was then scored with either a '+' (better on true than on untrue pairings), '0' (equal performance on the true and untrue pairings), or a '−' (better on the untrue than the true pairings). P.H. was significantly better at learning the true than the untrue pairings with the faces ($n = 9$, $x = 0$, one-tailed $P < 0.005$), the cars ($n = 9$, $x = 1$, one-tailed $P < 0.05$), and the flowers ($n = 8$, $x = 1$, one-tailed $P < 0.05$).

TABLE 4. LEARNING TRUE AND UNTRUE NAMES TO FACES, CARS AND FLOWERS

	Trial number											
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Faces												
True pairings	1	3	2	2	3	1	3	1	3	3	2	2
Untrue pairings	1	1	1	2	0	1	0	0	1	0	1	1
Cars												
True pairings	2	2	1	1	1	2	2	2	1	2	3	2
Untrue pairings	1	1	0	2	0	1	2	0	1	1	2	2
Flowers												
True pairings	2	3	3	3	2	3	1	3	3	2	3	3
Untrue pairings	1	2	3	1	2	1	2	2	2	2	3	2

Number of correct choices (max = 3) to match a stated name on each trial. Untrue pairings are created by interchanging the names of the items.

Discussion. The results of these tasks are clear-cut. P.H. found it easier to learn true than untrue picture-name combinations for photographs of faces, cars or flowers, thereby confirming the suggestion that his covert visual recognition was not restricted to face stimuli. This was found despite the fact that the recognition of faces demands identification of a ***unique individual***, whereas for cars and flowers we used tasks which only required assignment of the visual stimulus to a subordinate taxonomic group (*a* daffodil, *a* Volkswagen 'beetle', etc.). P.H.'s covert abilities covered all the categories we tested, with nothing in the results to suggest that they would not extend to all stimuli which are compromised by his overt recognition deficit.

An intriguing question concerns the relation between the covert recognition effects found in the picture-name learning tasks and the forced-choice name decision tasks. Are they different manifestations of the same underlying cause, or do they arise in different ways? Notice that the stimuli used in the learning experiments were ones for which P.H. had chosen the incorrect name in the forced-choice name decision task used to screen the items for any possibility of successful recognition. However, in the learning experiments the untrue names were not those which he had incorrectly accepted earlier in the forced-choice screening task. Instead, the names of all 3 celebrities allotted to the untrue condition were interchanged with each other. This led us to wonder whether there would be any covert recognition effect in the learning experiment if the untrue names used with each stimulus were those which P.H. had (incorrectly) accepted in the forced-choice name decision screening task. If the covert recognition effects found in learning and forced-choice name decision tasks have a common basis, one would expect this procedural change to eliminate the covert effect in the learning task, since further benefit should not accrue from the same source.

Learning true names and previously accepted foils to pictures

This experiment again involved teaching P.H. true and untrue names to pictures of familiar faces, cars and flowers. In contrast to the procedure used previously, however, the untrue names attached to the stimuli consisted of the alternatives P.H. had accepted in the forced-choice name decision pre-test used to screen suitable items.

Procedure. The procedure followed the one described in the previous experiment, except for the name selection in the untrue condition. Instead of exchanging names across stimuli in the untrue condition, the foils which P.H. had accepted in the forced-choice name decision pre-test were used as untrue names.

Results. The data for all three conditions are summarized in Table 5. For details of the data analysis we refer to the procedure used in the previous picture-name learning experiments. The difference between the true and untrue conditions failed to approach statistical significance with all three types of stimuli: faces ($n = 9$, $x = 4$, $P > 0.1$), cars ($n = 7$, $x = 3$, $P > 0.1$) and flowers ($n = 6$, $x = 3$, $P > 0.1$).

TABLE 5 LEARNING TRUE AND UNTRUE NAMES TO FACES, CARS AND FLOWERS

	Trial number											
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*
Faces												
True pairings	2	3	2	1	1	3	2	1	1	2	2	2
Untrue pairings	1	2	1	2	1	2	3	2	2	1	2	2
Cars												
True pairings	1	1	0	1	1	1	2	2	0	1	3	1
Untrue pairings	0	0	0	0	2	1	2	2	2	1	2	3
Flowers												
True pairings	2	1	2	1	2	2	2	2	1	2	3	3
Untrue pairings	1	1	1	1	3	2	2	3	1	3	3	2

Number of correct choices (max = 3) of item to match a stated name on each trial The untrue names are those which P.H had incorrectly accepted in a forced-choice name decision task.

Discussion. When the untrue names in the picture-name learning task were those which P.H. had accepted in the forced-choice name decision pre-test, the covert recognition effect disappeared completely in the learning experiments. This finding demonstrates that the covert recognition effects found in the forced-choice name decision and picture-name learning tasks could have a common basis, since no further benefit was found for items screened and then combined in this way. Of course, it is possible that investigations with other patients may reveal a different pattern. This remains to be seen In the meantime, our findings with P.H. point toward a potential common basis for covert recognition effects elicited by forced-choice name decision task and picture-name learning tasks.

This disappearance of the covert recognition effect held for faces, cars and flowers, which again emphasizes the comparability of P.H.'s impairment in the recognition of faces and other within-class stimuli: the presence and absence of covert recognition effects are dependent on the same experimental manipulations.

From covert to overt recognition

One exciting prospect of covert recognition is the possibility of using this in remedial work. If it were possible to make the outputs of these processes, which continue to operate covertly, accessible to the patient in some way an important relief of deficit could follow. Covert processing has been demonstrated in a wide range of cognitive impairments (Weiskrantz, 1986; Schacter *et al.*, 1988; Young and De Haan, 1990), and progress in this context could effect a major step forward in cognitive rehabilitation.

Because P.H. displayed such clear covert visual recognition effects on a wide range of tasks, he was a prime candidate for exploring potential ways of making his preserved covert knowledge overtly accessible to him. Two different procedures were employed to this end: repeated test administrations, and category presentations of visual stimuli.

Repeated administrations

The first method was suggested by Shallice (personal communication), and involved repeated overt identification responses to familiar faces, such as the discrimination between politicians' and entertainers' faces. We know that P.H. was initially unable to perform such a task, but the hypothesis was that numerous repetitions of the same task might elicit a steady improvement in performance. The idea behind this suggestion is that it might be useful to consider P.H.'s problem as a form of semantic access impairment. Warrington and Shallice (1979) and Shallice (1987) have made a distinction between modality-specific impairments in which the stored representations are themselves damaged and those in which there is a problem of access to an otherwise intact store. Shallice (1987) suggests a number of criteria for distinguishing between 'degraded store' and 'access' deficits, one of which is that for semantic access impairments continuous exposure to the same stimuli with the same task-requirement can 'warm up' previously inaccessible representations.

Procedure The stimuli were 2 sets of 10 face-photographs. In each set half of the faces were of famous politicians, the other half were entertainers (e.g. actors, television presenters, comedians).

To set a baseline of performance both sets were presented once to P H., with the politicians and entertainers in a pseudo-random order, for a politician versus non-politician decision to each face (P.H. was asked to say 'yes' if the face was that of a politician, 'no' to a non-politician). Subsequently, the stimuli of set 1 were presented 20 times, each time in a different pseudo-random order, with P.H. again performing the politician decision to each face. Finally, set 2 was given again, to check whether any increase in performance to set 1 was due to an activation effect, or some other non-specific effect as a result of repeating the procedure.

The number of stimuli in each set was kept small in order to increase the chance that P.H. might show an effect of repetition (by maximizing the possibility that particular representations could be 'warmed up'). At no time was any feedback given. This would have confounded the interpretation, because it would then be possible that P.H had simply learned to associate the photographs with the correct occupation during the task.

Results. During the whole procedure P.H. claimed to be guessing, and when questioned after the test he denied having experienced any increase in confidence during the repeated runs. The results are presented in Table 6, and it is clear that there was no evidence for increased accuracy across the repeated presentations. He consistently performed at chance level (mean performance on the 20 repeated trials of set 1 = 5.2 correct; SD = 1 0), without any indication of improvement.

Discussion. Our first attempt to convert preserved covert face recognition into overt recognition failed. During the repeated tests where P.H. was asked to discriminate between a small number of faces of politicians and non-politicians, there was no indication of increased accuracy. It would seem that the comparison with semantic access impairments is not a fruitful one to pursue for P.H. The results are, however, useful in demonstrating that mere repetition is not sufficient to restore overt recognition.

TABLE 6 POLITICIAN VERSUS NON-POLITICIAN DECISION TASK

	B	*Repetitions*																				F
		1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*	*19*	*20*	
Set 1:	5	4	5	6	4	6	4	4	7	5	6	6	5	4	6	5	6	5	5	4	7	
Set 2:	5																					6

Number correct (max = 10, chance = 5) on politician versus non-politician decision task for sets 1 and 2 on baseline (B) trials with sets 1 and 2, 20 repetitions of set 1, and one final repetition of set 2 (F)

Category presentation

Using the method we have called 'category presentation', Sergent and Poncet (1990) were successful in provoking *overt* recognition in prosopagnosia, with the effect being dependent on whether the patient could spontaneously determine the relevant category. Overt recognition was specific to this particular experimental procedure. We decided to explore the phenomenon with P.H.

Procedure. For the exploration of the category presentation effect in P.H. we used 6 categories. Three of these were 'broad' categories (politicians, television presenters, and comedians), and 3 were 'narrow' (actors in the television soap operas Neighbours, EastEnders and Coronation Street). There were 8 exemplars in each category. The terms broad and narrow refer to the extent to which the exemplars of the category are associated with one another. This manipulation was included in the experiment because we thought that it might be relevant to Sergent and Poncet's (1990) observation that the effect was not present for all categories in P.V.

The first (pre-test) phase of the experiment involved presentation of all the faces one at a time, in a pseudo-random order, for overt recognition. Subsequently, the 8 exemplars of each category were presented together in the following order: Politicians, EastEnders, Coronation Street, Television presenters, Comedians, and Neighbours. In the first instance P.H. was asked to tell everything he could about these people. Subsequently, he was told that the faces he was being shown belonged to people with 'the same job', and he was asked to try to identify them. If he still failed to identify them, he was told the category, and asked again to try to identify them. This formed the 'category presentation' condition. Subsequently, the first phase was repeated with a different presentation order on two occasions; one immediately after the category presentation condition (immediate post-test), and one after about 2 mths (delayed post-test).

Results. The results are presented in Table 7. Our criterion for correct overt recognition is naming the face or giving appropriate and detailed semantic information.

TABLE 7 OVERT IDENTIFICATIONS BY P H IN THE CATEGORY PRESENTATION TASK

					Post-test			
	Pre-test		*Category presentation*		*Immediate*		*Delayed*	
	+	−	+	−	+	−	+	−
Broad categories								
Politicians	0	0	0	0	0	0	0	0
TV presenters	0	0	0	0	0	4	0	1
Comedians	2	2	1	0	2	2	1	0
Narrow categories								
Neighbours	0	0	1	0	1	0	0	0
EastEnders	1	0	6	0	5	0	1	0
Coronation Street	0	0	1	0	1	1	0	0

Number (max = 8) of correct (+) and incorrect (−) overt identifications by P.H. in the different conditions of the category presentation task. These involved a pre-test with the faces in pseudo-random order, simultaneous presentation of all 8 faces from a particular category, and immediate and delayed post-tests with pseudo-random ordering.

In the pre-test, P.H. was unable to identify most of the faces. He named 2 faces correctly (Ronnie Corbett and Ken Dodd) and gave the correct occupation for another one, but for two other faces he gave an incorrect occupation and all his other responses (43) were 'don't know'. With the category presentation procedure, there was little improvement in 5 of the 6 categories. In 3 of these P.H. did recognize 1 of the exemplars, and this would have been enough for him to know the occupation of all other members, after he had been told that they all had the same job. However, this information did not elicit any more identification.

On the 'EastEnders' category, though, P.H.'s behaviour mirrored that of Sergent and Poncet's (1990) patient in the category presentation condition. Once he had spontaneously established the occupation of

1 of the exemplars, he started to recognize more, until he had identified 6 of the 8 faces. Notice too that he did not make any misidentifications of faces from this category, which suggests that he was not simply guessing on the basis of superficial cues (age, sex. etc.) and the knowledge that all faces came from this soap opera.

In the immediate post-test, P H. showed substantial savings from his improved performance on the category presentation condition. He recognized 5 of the 6 EastEnders again. However, he had returned to baseline on the delayed post-test given some 2 mths later.

Discussion. The main conclusion from these findings is that P.H. did show the beneficial effect of simultaneous presentation of celebrities with a common occupational background described by Sergent and Poncet (1990) in their patient P.V. This was the first time since we started working with him (5 yrs ago) that he confidently recognized several photographs of familiar faces. This phenomenon will warrant further exploration, given its possible impetus to remedial work.

There were, however, two differences between P.H. and P.V. First, the phenomenon was convincingly observed for only 1 category in P.H., despite the inclusion of 3 'narrow' categories in our experiment. The fact that the category for which P.H. showed improved overt recognition was a narrow category indicates that the degree to which the exemplars are associated with one another might be important in producing the effect. The absence of improvement in the other narrow categories may be explained by less familiarity with the celebrities, since P.H. commented that he did not follow these programmes (e.g. Coronation Street: 'it was ages ago since I saw that').

The second difference was that P.H. did show some savings on the immediate post-test, where the stimuli of all categories were mixed and presented again individually. This was not found for P.V. P.H.'s savings had disappeared on subsequent testing 2 mths later, but the fact that the provoked recognition was less transient for P.H. than P.V. again points to its potential remedial importance.

Of course, any effective remedial technique based on such procedures is still a long way off, and will depend on knowing much more about the conditions under which overt recognition can be provoked and, above all, maintained. All we have done here is to demonstrate a fairly short-lived effect with a category (EastEnders) that is not really of high ecological significance. But this initial finding is more promising than anything that has emerged from more conventional training procedures (e.g. Ellis and Young, 1988).

GENERAL DISCUSSION

Covert face recognition has now been established in a number of patients with a variety of techniques. As a consequence, research has shifted from demonstrating the phenomena associated with covert recognition towards a more analytical exploration of their nature. The present findings contribute to four separable issues. These concern covert recognition in direct and indirect tests, the breakdown of within-class recognition, remedial implications, and the clinical pattern accompanying covert recognition in prosopagnosia.

Covert recognition in direct and indirect tests

A particularly appealing hypothesis has been that covert recognition is found in indirect tests, whereas direct tests demonstrate the patients' overt recognition impairments. The present findings, and those of Sergent and Poncet (1990) show that this is too simple a characterization. It is now clear that there are some direct tests which can engage preserved, covert abilities.

Both P.H. and P.V. (Sergent and Poncet, 1990) performed consistently above chance level when they were asked to choose the name that matched a photograph of a familiar face from correct and incorrect alternative names. Although the patients commented that they were continually guessing, two alternative explanations needed to be excluded before this above-chance performance of a direct test could be attributed to covert face recognition.

First, we demonstrated that P.H. was unable to form mental images of the faces of known people. Thus we ruled out the possibility that he was creating an internal image for each of the 2 celebrities whose name was given, and matching these against the presented photograph.

The second problem concerned the reliability of the patients' testimony that they were guessing 'all the time'. Adapting the procedure developed by Sergent and Poncet (1990), we showed that P.H. was unaware of the information which allowed him to perform above chance level. When the original task with 1 correct and 1 incorrect name alternative was changed to one where both names were incorrect, P.H. continued to choose a name, oblivious to the fact that no correct answer was possible. In addition, his confidence ratings were the same whether the task included a correct name alternative or not. Therefore, we concluded (like Sergent and Poncet, 1990) that forced-choice name decision tasks *can* show covert recognition effects, even though a direct test is involved, and that P.H. and P.V. are comparable in that they both show covert face recognition on this type of task.

What is it about forced-choice name decision which successfully engages covert recognition abilities? We cannot be certain at present, but there are some pointers. It is not simply the use of forced-choice, since we showed previously that P.H. was at chance level on another forced-choice task, which involved deciding which of two faces is familiar (Young and De Haan, 1988). A more promising possibility is that a number of the tasks which elicit covert recognition, for P.H. and other patients, seem to rely on some form of interaction between face and name recognition systems (*see* Young and De Haan, 1988). Examples include Bauer's (1984) application of the 'guilty knowledge' test, and our semantic priming, interference, and learning paradigms (De Haan *et al.*, 1987*a,b*; Young *et al.*, 1988). Since forced-choice name decision involves both face and name inputs, it may tap into this interaction.

This view is strengthened by the fact that we were able to demonstrate that the covert recognition effects found in forced-choice name decision and in picture-name learning tasks may have a common basis. This was evident because no further learning task benefit was possible for items screened and then combined in such a way that the untrue names in the picture-name learning task were those which P.H. had already accepted in a forced-choice name decision pre-test.

Breakdown of within-class recognition

P.H.'s visual recognition deficit extended to other within-class discriminations than faces. He was also extremely poor at overt identification of cars or flowers. However, on a forced-choice name decision task where he was asked to choose between two alternative names for a picture of a face, car or flower, P.H. performed above chance level for all three stimulus classes. Subsequently, he was also shown to be significantly better at learning true than untrue picture-name pairings for all these classes of stimuli. Therefore, it can be concluded that there is covert recognition of faces, cars and flowers for P.H.

The implications of this finding of covert recognition for all stimulus classes tested with P.H. need to be carefully considered. Certainly, had we found covert effects for faces only, this would have supported claims (*reviewed by* Ellis and Young, 1989) that a specialized face recognition mechanism exists. However, our finding of similar effects across stimulus classes does not necessarily invalidate this hypothesis. What it does demonstrate is that the functional nature of P.H.'s overt recognition deficit is equivalent across these classes of stimuli. Although unparsimonious, this might be due to coincidentally equivalent impairments of separate mechanisms for face recognition and other types of within-class recognition. We must accept that whilst our findings of covert recognition of other stimulus classes than faces are consistent with the idea that a common deficit is involved, they do not prove it.

The reason we are so cautious with this conclusion is that we are aware of the evidence of dissociations between within-class impairments of overt recognition found in some other cases (e.g. Bruyer *et al.*, 1983; Assal *et al.*, 1984; De Renzi, 1986; *reviewed by* Ellis and Young, 1989). Although the present results lend no support to the idea of a specialized recognition system for faces alone, it would be unwise to reject this possibility until there is a convincing account of these dissociable impairments that does not require separate specialized systems for within-class recognition of different types of stimuli.

Remedial implications

Face recognition impairments are very disabling, and one of the aims of our work has been to begin to explore the promise of different possible methods with remedial implications. Glisky *et al.*'s (1986) successful application of remedial procedures (method of vanishing cues) based on implicit memory, to teach an amnesic computer skills, underlines the potential practical applications of covert recognition.

Two procedures were investigated here. One involved repeated presentations, and was based on the idea that it might be useful to consider P.H.'s problem as a form of semantic access impairment (Warrington and Shallice, 1979; Shallice, 1987). However, this was unsuccessful in effecting any improvement of overt recognition, suggesting that this may not be the correct parallel to pursue for P.H.

The second procedure was based on Sergent and Poncet's (1990) finding of overt face recognition in prosopagnosia when a number of famous faces from the same occupational category were simultaneously presented. Like P.V., P.H. did achieve overt recognition of some faces with this 'category presentation' procedure. Interestingly (and unlike P.V.), this overt recognition persisted in our immediate post-test with P.H., even though the faces were then presented one at a time in pseudo-random order. It is encouraging that, once provoked, overt recognition showed some persistence across time and testing conditions for P.H., but obviously further work will be needed to explore the limits of this, and its practical usefulness.

Sergent and Poncet's (1990) category presentation method shows that the loss of overt recognition in prosopagnosia need not be insuperable. They suggest that 'neither the facial representations nor the semantic information were critically disturbed in P.V., and her prosopagnosia must thus reflect faulty connections between faces and their memories, perhaps characterized by a heightened threshold of activation of the information that underlies conscious recognition'. Sergent and Poncet (1990) hypothesize that the simultaneous presentation of several members of the same category may temporarily raise the activation level above the appropriate threshold. Presenting the patient with the category-name (if he or she fails to recognize it spontaneously) does not result in identification, which implies that the bottom-up activation of semantic (category) information is crucial in provoking overt recognition.

The clinical pattern accompanying covert recognition in prosopagnosia

We have noted that a number of the investigations reported here demonstrated parallels between the patients P.V. (Sergent and Poncet, 1990) and P.H. Both showed substantial effects of covert face recognition on forced-choice name decision and true versus untrue paired associate learning tasks, and both displayed some overt recognition when the faces of a number of associated celebrities were presented simultaneously (category presentation). Examining the case descriptions of these patients also makes it apparent that they show a similar clinical pattern, despite the obvious difference in aetiology.

P.H. suffered a severe closed head injury, whereas P.V. contracted encephalitis. Neuro-imaging showed substantial lesions in the posterior right hemisphere and some additional damage to the left hemisphere in both cases. Neither patient had a visual field defect or a colour perception impairment. Both patients had relatively preserved language functions, but memory functions were substantially affected. Finally, within-class recognition problems were apparent in both cases.

Prosopagnosia is a rare symptom, but from the literature it is clear that some features of this clinical constellation are unrepresentative, especially the absence of a left upper quadrantanopia and achromatopsia and the presence of an amnesic deficit (*see* Meadows, 1974). It seems that there is a certain type of prosopagnosia which is characterized by relatively intact perception, visual memory problems and covert visual recognition. Future research must now establish the extent to which these patients can be helped with remedial procedures which make use of their preserved face processing abilities.

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REFERENCES

ASSAL G, FAVRE C, ANDERES, JP (1984) Non-reconnaissance d'animaux familiers chez un paysan: zoo-agnosie ou prosopagnosie pour les animaux. *Revue Neurologique*, **140**, 580–584.

BAUER RM (1984) Autonomic recognition of names and faces in prosopagnosia: a neuropsychological application of the Guilty Knowledge Test. *Neuropsychologia*, **22**, 457–469.

BAUER RM (1986) The cognitive psychophysiology of prosopagnosia. In: *Aspects of Face Processing*. Edited by H. D. Ellis, M. A. Jeeves, F. Newcombe and A. Young. Dordrecht: Martinus Nijhoff, pp. 253–267.

BAUER RM, VERFAELLIE M (1988) Electrodermal discrimination of familiar but not unfamiliar faces in prosopagnosia. *Brain and Cognition*, **8**, 240–252.

BENTON AL, VAN ALLEN MW (1973) *Test of Facial Recognition. Manual.* Neurosensory Center Publication No. 287. Ames, IA: University of Iowa.

BODAMER J (1947) Die Prosop-Agnosie. (Die Agnosie des Physiognomieerkennens). *Archiv für Psychiatrie und Nervenkrankheiten*, **179**, 6–53.

BRUYER R, LATERRE C, SERON X, FEYEREISEN P, STRYPSTEIN E, PIERRARD E *et al.* (1983) A case of prosopagnosia with some preserved covert remembrance of familiar faces. *Brain and Cognition*, **2**, 257–284.

DAMASIO AR, DAMASIO H, VAN HOESEN GW (1982) Prosopagnosia: anatomic basis and behavioral mechanisms. *Neurology, New York*, **32**, 331–341.

DE HAAN EHF, YOUNG A, NEWCOMBE F (1987*a*) Faces interfere with name classification in a prosopagnosic patient. *Cortex*, **23**, 309–316.

De Haan EHF, Young A, Newcombe F (1987*b*) Face recognition without awareness. *Cognitive Neuropsychology*, **4**, 385–415.

De Renzi E (1986) Current issues on prosopagnosia. In: *Aspects of Face Processing*. Edited by H. D. Ellis, M. A. Jeeves, F. Newcombe and A. Young. Dordrecht: Martinus Nijhoff, pp. 243–252.

Duensing F (1952) Beitrag zur Frage der optischen Agnosie. *Archiv für Psychiatrie und Nervenkrankheiten*, **188**, 131–161.

Ellis HD, Young AW (1988) Training in face-processing skills for a child with acquired prosopagnosia. *Developmental Neuropsychology*, **4**, 283–294

Ellis HD, Young AW (1989) Are faces special? In: *Handbook of Research on Face Processing*. Edited by A W. Young and H. D. Ellis. Amsterdam. North Holland, pp. 1–26.

Farah MJ, Levine DN, Calvanio R (1988) A case study of mental imagery deficit. *Brain and Cognition*, **8**, 147–164.

Glisky EL, Schacter DL, Tulving E (1986) Computer learning by memory-impaired patients: acquisition and retention of complex knowledge. *Neuropsychologia*, **24**, 313–328.

Habib M (1986) Visual hypoemotionality and prosopagnosia associated with right temporal lobe isolation. *Neuropsychologia*, **24**, 577–582.

Hay DC, Young AW (1982) The human face. In: *Normality and Pathology in Cognitive Functions*. Edited by A. W. Ellis London: Academic Press, pp. 173–202.

Levine DN, Warach J, Farah M (1985) Two visual systems in mental imagery: dissociation of 'what' and 'where' in imagery disorders due to bilateral posterior cerebral lesions. *Neurology, Cleveland*, **35**, 1010–1018.

Meadows JC (1974) The anatomical basis of prosopagnosia. *Journal of Neurology, Neurosurgery, and Psychiatry*, **37**, 489–501.

Newcombe F, Young AW, De Haan EHF (1989) Prosopagnosia and object agnosia without covert recognition. *Neuropsychologia*, **27**, 179–191.

Renault B, Signoret J-L, DeBruille B, Breton F, Bolgert F (1989) Brain potentials reveal covert facial recognition in prosopagnosia. *Neuropsychologia*, **27**, 905–912.

Rizzo M, Hurtig R, Damasio AR (1987) The role of scanpaths in facial recognition and learning. *Annals of Neurology*, **22**, 41–45.

Sergent J, Villemure J-G (1989) Prosopagnosia in a right hemispherectomized patient. *Brain*, **112**, 975–995.

Sergent J, Poncet M (1990) From covert to overt recognition of faces in a prosopagnosic patient. *Brain*, **113**, 989–1004.

Schacter DL, McAndrews MP, Moscovitch M (1988) Access to consciousness: dissociations between implicit and explicit knowledge in neuropsychological syndromes. In: *Thought Without Language*. Edited by L. Weiskrantz. Oxford: Clarendon Press, pp. 242–278.

Shallice T (1987) Impairments of semantic processing: multiple dissociations. In: *The Cognitive Neuropsychology of Language*. Edited by M. Coltheart, G. Sartori and R. Job. London: Lawrence Erlbaum, pp. 111–127.

Tranel D, Damasio AR (1985) Knowledge without awareness: an autonomic index of facial recognition by prosopagnosics. *Science*, **228**, 1453–1454.

Tranel D, Damasio AR (1988) Non-conscious face recognition in patients with face agnosia. *Behavioural Brain Research*, **30**, 235–249.

Warrington EK, Shallice T (1979) Semantic access dyslexia. *Brain*, **102**, 43–63.

Weiskrantz L (1986) *Blindsight: A Case Study and Implications*. Oxford: Oxford University Press.

Young AW, De Haan EHF (1988) Boundaries of covert recognition in prosopagnosia. *Cognitive Neuropsychology*, **5**, 317–336.

Young AW, Hellawell D, De Haan EHF (1988) Cross-domain semantic priming in normal subjects and a prosopagnosic patient. *Quarterly Journal of Experimental Psychology*, **40A**, 561–580.

Young AW, Ellis HD (1989) Childhood prosopagnosia. *Brain and Cognition*, **9**, 16–47.

Young AW, De Haan EHF (1990) Impairments of visual awareness. *Mind and Language*, **5**, 29–48.

Young AW, De Haan EHF (1991) Face recognition and awareness after brain injury. In: *The Neuropsychology of Consciousness and Cognition*. Edited by A. D. Milner and M. D. Rugg. London: Academic Press, pp. 69–90.

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DIFFERENTIAL IMPACT OF RIGHT AND LEFT HEMISPHERE LESIONS ON FACIAL EMOTION AND OBJECT IMAGERY

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SUMMARY

Thirty-six patients with unilateral hemispheric lesions of the right hemisphere (RHD), left hemisphere (LHD), or no neurologic disease were evaluated on two tasks of visual imagery: one involved imagery for facial emotions and the other involved imagery for common objects. As a group, the RHD patients were more impaired on the emotional than the object imagery task, whereas the LHD patients showed the opposite pattern. Individual case analyses suggested that the RHD group consisted of different behavioural subtypes One patient with a right inferior occipito-temporal lesion had a facial emotion imagery generation defect, other RHD patients displayed a facial affect agnosia (being impaired on emotional imagery and emotional perceptual tasks), while other RHD patients had perceptual defects with sparing of imagery performance. A final RHD group was globally impaired across all imagery and perceptual tasks. These findings support the hypothesis that the right hemisphere may contain a 'lexicon' of facial emotions. Furthermore, these findings argue against current views that it is exclusively the left or right hemisphere that mediates visual imagery. Rather, hemispheric asymmetries in imagery performance are to some extent material-representation specific and may arise when (*a*) the representations of objects/events to be imaged are differentially represented in the hemispheres, and/or (*b*) when the operations acting on these imaged events are differentially lateralized.

INTRODUCTION

Neuropsychological studies over the past 15 years have established that the right hemisphere is intimately involved in the perception and interpretation of non-verbal emotional signals. One general finding has been that patients with right hemisphere damage (RHD) are more impaired in identifying emotional facial expressions and emotional prosody than are their left hemisphere-damaged (LHD) counterparts (for reviews, *see* Etcoff, 1989; Heilman and Bowers, 1990). Because many RHD patients have co-existing disturbances in processing visuospatial stimuli and complex auditory harmonics, it has been argued that these 'more basic' or elemental defects underlie their impaired ability to identify emotional signals. Counter arguments to this view have been based on group studies that have statistically adjusted for visuoperceptual abilities (Ley and Bryden, 1979; Bowers *et al.*, 1985), and on case descriptions in which 'dissociations'

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between the performance on visuoperceptual versus visuoaffective tasks have been noted. Namely, some RHD patients perform 'normally' when asked to distinguish between two neutral unfamiliar faces, yet nevertheless display dramatic defects when asked to identify emotional facial expressions (Dekosky *et al.*, 1980).

Recently, Blonder *et al.* (1991) found that RHD patients were impaired [relative to mildly aphasic LHD or normal controls (NHD)] in identifying the emotion associated with a verbal description of a non-verbal signal. In this study, patients were read brief statements describing facial ('he scowled'), vocal ('she laughed'), or gestural signals ('he shook his fist'). Because these signals were verbally described, the poor performance of the RHD group could not be attributed to perceptual disturbance. Likewise, it was not due to a more widespread disturbance in 'emotional knowledge', as RHD patients performed normally when asked to make inferences about situations that are prototypically linked to various emotions. Rather, the poor performance of RHD patients in assigning an emotion to a verbally-described non-verbal signal suggested that the right hemisphere may contain neural 'representations' of species-typical facial expressions, gestures and prosodic contours (Blonder *et al.*, 1991).

The question of whether there is a 'vocabulary' of emotional signals resident in the right hemisphere is clearly an important one and is analogous in some respects to the notion of the left hemisphere's verbal lexicon. We have previously proposed that the right hemisphere may contain a 'lexicon' of facial expressions (Bowers and Heilman, 1984). In our view, this lexicon consists of structural prototypes of various facial emotions. In essence these prototypes are long-term memory (LTM) 'representations' that, in our model (Fig. 1), are interconnected with other areas that endow them with meaning (verbal semantics, emotional semantics). Apart from findings that RHD patients are generally impaired on facial affect tasks, evidence for the existence of these facial prototypes and their right hemisphere locus is indirect. It derives from logically considering the components of this model (lexicon, semantics, interconnections between them) and the patterns of performance competencies displayed by patients on tasks designed to assess these components. This type of approach is currently popular among

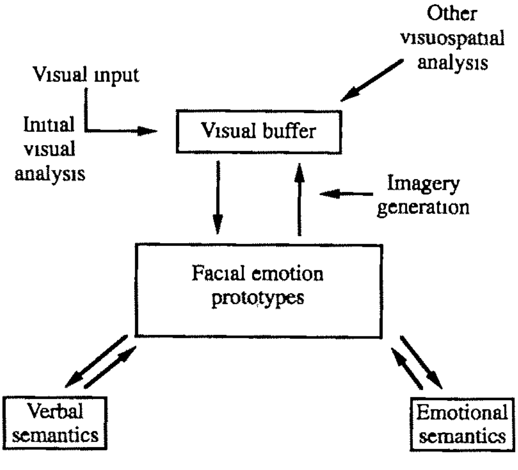

FIG. 1. Diagrammatic representation of the systems mediating the discrimination, recognition and imagery of emotional faces.

cognitive neuropsychologists (Farah, 1984; Caramazza, 1986; Ellis and Young, 1988; Semenza *et al.*, 1988; Shallice, 1988).

In line with this approach, we have previously proposed (Bowers and Heilman, 1984) that destruction of the facial emotion lexicon and/or its connections with other areas that endow it with meaning (verbal semantics, emotional semantics) should induce a variety of deficits in processing facial emotions. In fact, different 'syndromes' of facial affect processing should occur depending on which components are disrupted. Specifically, when the facial emotion prototypes themselves are destroyed or degraded, a facial affect agnosia should occur. In this situation, patients would be unable to discriminate, name, sort or select prototypical facial expressions. An anomic type of defect would occur when the connections between the facial emotion lexicon and verbal semantics are disrupted. Such patients would be unable to name facial expressions or select named prototypes (point to the happy face), yet perform normally when sorting or matching facial emotions. Cases of this sort, which can be viewed as category-specific visual-verbal disconnections, have been described by Bowers and Heilman (1984) and more recently by Rapcsak *et al.* (1989).

Given this framework, selective defects in 'imaging' facial emotions should also exist in certain RHD patients. An underlying assumption in this situation is that one must access 'LTM' representations of facial emotion in order to image them. This is a view that is generally, although not universally, held by proponents of various cognitive models of imagery, such as that proposed by Kosslyn (1980, 1987). In Kosslyn's (1980, 1987) imagery model, the ability to form mental images requires two major components. The first component is structural in nature and involves the LTM representations of the visual/spatial characteristics of objects. The second component involves a generative process by which these 'representations' are activated and transformed into a consciously experienced short-term mental image. For Kosslyn, the result of this imagery generation process is to array the imaged event in a short-term visual 'buffer', where it can undergo additional spatial analyses.

If our view that the right hemisphere contains a lexicon/representation of facial emotions is correct, then one would expect RHD patients to perform poorly on tasks requiring them to access these representations in order to image them. Further, the locus of the deficit in imaging facial emotions should vary, depending on the integrity of the facial emotion lexicon. For example, when the facial emotion 'representations' themselves are destroyed, RHD patients should have difficulty both in imaging facial emotions and in identifying visible emotional faces. In contrast, other RHD patients would be predicted to display isolated deficits in imaging emotional facial emotions. In such patients, their lexicon of facial emotions would be intact, although their ability to place these 'face-icons' into the visual buffer where they could be pictured in the 'mind's eye' would be disrupted. In the language of Kosslyn (1980), this would be akin to a defect in 'imagery generation', although it would be specific for facial expressions.

The purpose of the present study was threefold. First, we wanted to determine whether RHD patients as a group had difficulty in performing a facial emotion imagery task. To assess this, patients with focal lesions of the right or left hemisphere were given a task that involved imagery for facial expressions. To determine whether defective imagery for facial expressions merely reflected one instance of a more global imagery disturbance, subjects were also given a task that involved imagery for objects, animals and people. Secondly, we wanted to determine whether defects in imaging facial expressions always co-occurred with defects in identifying visible facial expressions or whether 'dissociations' might exist. That is, would some patients be impaired in imaging facial emotions, yet have no difficulty in making judgements about visible emotional faces (or vice versa). To address this possibility, performance on the emotional imagery task was compared with performance on perceptual tasks involving judgements of facial affect and facial identity. Thirdly, we wanted to determine, on a case-by-case basis, whether individual patients displayed different patterns of performance across the emotional imagery and emotional perceptual tasks and whether these patterns corresponded to lesions in specific neuroanatomic sites.

METHODS

Subjects

The subjects were 36 right-handed patients seen either at Shands Teaching Hospital of the University of Florida or the Department of Veterans Affairs Medical Center in Gainesville, FL. They consisted of 12 patients (11 males, 1 female) with infarctions confined to the right hemisphere (RHD), 12 patients (11 males, 1 female) with infarctions of the left hemisphere (LHD), and 12 patients (11 males, 1 female) without neurologic disease who had a history of orthopaedic illness (NHD). Seven of the 12 RHD patients had extinction and/or neglect. All the LHD patients were aphasic but had relatively mild language comprehension defects. Aphasia quotients derived from the Western Aphasia Battery (Kertesz, 1982) ranged from 60 to 93.6. The LHD patients were classified into aphasic subgroups (n = 3 anomics, n = 3 conduction aphasics, n = 6 Broca's aphasics) on the basis of performance on the Western Aphasia Battery and the Boston Naming Test (Goodglass *et al.*, 1983). The groups did not differ in terms of age or education, and the two brain impaired groups did not differ with respect to the interval between their stroke and time of testing. Patient characteristics, including lesion localization derived from MRI and CT scans, are depicted in Table I.

Experimental tasks

All subjects received two tasks of visual imagery; one involved imagery for facial emotions and the second involved imagery for common objects. In addition, subjects were given two perceptual tasks to assess their processing of visible facial stimuli, both emotional and neutral. Approximately half the subjects within each group received the imagery tasks first and the remaining subjects received the perceptual tasks first.

Imagery tasks

The imagery tasks, described below, consisted of a series of questions about the structural characteristics of objects or facial expressions. During the imagery tasks, subjects never actually viewed these stimuli (objects, expressions), but had to answer questions based on their own 'internal representation' of these events. Presumably, they had to access this internal representation (i.e. expression lexicon) and then 'image' its visual/structural properties. Half of the subjects within each group received the emotional imagery task first and the remaining received the object imagery task first.

Imagery for emotional facial expressions. In this task, subjects were asked to imagine that they were looking at the face of someone who was displaying a target emotion (e.g. 'imagine that you are looking at the face of someone who is very happy'). They were then asked a series of eight yes/no questions about the way the person's face looked. Four different imagery conditions were given, each involving a different emotion (happiness, sadness, anger, fear). A total of 32 questions was asked, eight for each of four emotions. These questions had been given a group of normal college students (n = 12) who were asked to judge the extent to which they relied on visual imagery to answer them. A five-point rating scale was used (1 = no

TABLE PATIENT CHARACTERISTICS

Case no	Age	Sex	Education	Months since CVA	CT/MRI lesion location	Clinical symptoms: Hemiparesis	Aphasia*	Neglect
RHD group								
1	67	M	14	05	R. frontoparietal	+	–	+
2	52	M	12	76	R. frontotemporal insula	+	–	–
3	61	M	12	09	R. frontotemporal parietal insula	+	–	+
4	70	M	18	159	R frontotemporal parietal	+	–	+
5	62	M	12	44	R temporoparietal	–	–	–
6	67	M	15	12	R frontotemporal parietal	+	–	+
7	70	M	15	63	R. occipitotemporal	–	–	–
8	66	M	16	29	R frontotemporal parietal, insula	–	–	+
9	64	M	05	09	R frontotemporal occipital	+	–	–
10	62	M	08	01	R. frontotemporal parietal	–	–	+
11	55	M	08	03	R. frontotemporal parietal	+	–	–
12	57	F	14	02	R. temporoparietal	–	–	+
LHD group								
1	72	M	14	135	L. parietotemporal occipital	–	Conduction	–
2	61	M	09	111	L frontotemporal parietal	+	Broca	–
3	64	M	14	41	L frontotemporal parietal	+	Conduction	–
4	45	M	12	72	L. frontotemporal parietal	+	Broca	–
5	72	M	14	84	L. parietotemporal insula	–	Mild Broca	–
6	45	M	15	01	L parietotemporal	–	Anomic	–
7	52	F	14	08	L parietotemporal	–	Anomic	–
8	59	M	13	24	L. frontotemporal parietal	+	Broca	–
9	63	M	15	02	L. temporal insula	–	Anomic	–
10	77	M	14	02	L temporal	–	Conduction	–
11	55	M	08	08	L frontotemporal parietal	+	Broca	–
12	55	M	10	161	L frontotemporal parietal	+	Broca	–

Mean age	Mean education	Months since stroke
RHD 62 7 (5 8)	RHD 12 4 (3 8)	RHD 34.3 (46.7)
LHD 60 0 (10 3)	LHD 12.5 (2 6)	LHD 55 0 (56 4)
NHD 65 0 (6 0)	NHD 12 5 (1.9)	NHD – –
NS	NS	NS

*Based on performance of the Western Aphasia Battery

imagery, 5 = high imagery). Imagery ratings ranged from 4 to 5, with a mean rating of 4.75 (SD = 0.45). Sample items are provided below.

Sample: Imagine that you are looking at the face of someone who is very frightened.

Do the eyes look twinkly?	Yes No
Is the brow raised?	Yes No
Are the eyes opened wide?	Yes No
Are the corners of the lips raised up?	Yes No

Object imagery task. This task was adopted from Eddy and Glass (1981) and consisted of 22 questions about the visual characteristics of objects, animals and people. The questions were read to the subjects. Presumably, subjects must 'image' the objects in order to answer the questions accurately. Sample items are depicted below.

What's higher off the ground, a horse's knee or the top of its tail?

Is a date on a penny toward the top or the bottom?

What's bigger, a thimble or a pencil eraser?

What number from one to ten does a peanut look like?

Perceptual facial tasks

The purpose of these tasks was to determine whether subjects had difficulty processing 'visually' presented facial stimuli, either emotional or neutral. In these tasks, subjects actually viewed facial stimuli and had to make judgements about them. Imagery *per se* was not involved. These perceptual facial tasks (i.e. discrimination of facial emotion, discrimination of facial identity) were a subset of a larger facial affect battery (*see* Bowers *et al.*, 1989) and were given in the same order to all patients. Discrimination of facial identity always preceded discrimination of facial emotion.

Discrimination of facial emotions. Subjects were shown pairs of unfamiliar faces and had to determine whether the two faces depicted the same or different emotional expression. A total of 20 trials was given. Each trial consisted of two photographs of two different actresses. The photographs were mounted vertically on a 12.5×7.5 cm card. On half the trials, the two actresses displayed the same facial emotions (i.e. 10 'same' trials). On the remaining trials, different facial emotions were displayed by the two actresses (10 'different' trials). The stimuli used in constructing this task derived from four different actresses, each of whom displayed five different emotions (happiness, sadness, anger, fear and indifference). Preliminary pilot work in our laboratory indicated greater than 90% agreement among a group of 30 elderly normals who rated the affects displayed by these faces.

Discrimination of facial identity. In this task, subjects were shown pairs of unfamiliar faces and asked to determine whether the two faces were the same or different persons. Twenty trials were given. Again, each trial consisted of two photographs, mounted vertically on a 7.5×12.5 cm card. On half the trials, identical photographs of the same person were shown (10 'same' trials). For the remaining trials, photographs of two different people were shown (10 'different' trials). All stimuli were photographs of women, without jewellery or glasses, who wore surgical caps to mask their hair. All had neutral facial expressions.

RESULTS

Performance on the imagery and the perceptual tasks was scored in terms of percent correct. Analysis of the results of the group data are presented first, followed by presentation of the individual case analyses.

Group data

Imagery tasks. The data (% correct) from the facial emotion and object imagery tasks were analysed using a repeated measure analysis of variance (ANOVA) with *group* (RHD, LHD, NHD) as the between-subject factor and *imagery task* (Emotional, Object) as the within-subject factor. Results revealed a significant main effect for group [F(2,33) = 8.58, $P < 0.001$]. Although the overall performance of the two brain impaired groups was comparable (LHD = 79.5%, RHD = 75.8%, $P > 0.05$), each was worse than the NHD group (X = 87.3%, $P < 0.01$). A significant Group×Task interaction [F(2,34) = 5.59, $P < 0.01$] was also obtained and is depicted in Fig. 2. *Post hoc* comparisons (Tukey HSD) indicated that the RHD group performed significantly worse on the facial emotion imagery task than on the object imagery task (Emotional = 71.9%, Object = 79.7%, $P < 0.05$). Eight of the 12 RHD patients showed this pattern. Conversely, the LHD group performed significantly worse on the object imagery task than on the facial emotion imagery task (Emotional = 83.8%, Object = 75.4%, $P < 0.05$). Eight of the 12 LHD subjects showed this pattern. In contrast, the NHD group achieved comparable performance across the object imagery and facial emotion tasks (Object imagery = 89.6%, Emotion = 91.8%). For the facial emotion task, the RHD group was significantly worse than the LHD group ($P < 0.05$), who did not differ from the normal controls (RHD = 71.9%, LHD = 83.8%, NHD = 91.8%). For the object

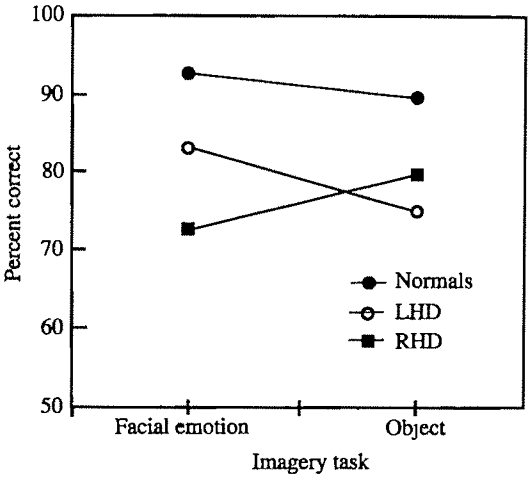

FIG. 2. Graphic representation of the performance by the RHD, LHD and normal groups on facial emotion and object imagery tasks

imagery task, the RHD and LHD groups were equally impaired, with both performing worse than the control group (RHD = 79.7%, LHD = 75.4%, NHD = 89.6%).

Because over half the RHD group (7 out of 12) exhibited features of neglect and/or extinction, additional analyses (t tests) were performed in which imagery performance of the RHD patients was examined as a function of neglect. Results of these analyses were non-significant. The performance of RHD patients with neglect did not differ from that of 'non-neglecting' RHD patients on either the object imagery task ($t = 1.40$, $P > 0.05$) or the facial emotion imagery task ($t = 0.79$, $P > 0.05$). Similarly, the imagery performance of the LHD patients was examined as a function of the severity of their language comprehension deficits (using scores from the sentence comprehension subtest of the WAB). This was done to address the concern that the object imagery questions might be more difficult to comprehend than the facial emotion questions on a purely linguistic/syntactic basis. Two types of analyses were carried out. In the first, a correlational analysis was performed and revealed that language comprehension scores did not significantly correlate with either object imagery performance ($r = 0.22$, $P > 0.05$) or with emotion imagery performance ($r = 0.12, P > 0.05$). Secondly, we examined the distribution of language comprehension scores among the LHD subjects (which ranged from 44 to 80, out of a possible 80) and divided it in half. This resulted in two subgroups of LHD subjects, those with lower versus those with higher language comprehension scores. Imagery performance was then analysed in these two aphasic subgroups using t tests. There were no significant differences in either object imagery scores ($t = 1.53, P > 0.05$) or emotion imagery scores ($t = 1.12, P > 0.05$) between those LHD subjects with lower versus higher language comprehension scores. Taken together, these results fail to support a relationship between imagery performance and language comprehension among our group of mildly aphasic LHD patients. These findings further suggest that the impaired performance of the LHD group on the object imagery was not related to difficulties in language comprehension *per se*.

Additional analyses were carried out to determine whether the RHD patients had specific difficulty 'imaging' certain facial emotions and not others. This was done using a repeated measures ANOVA in which *type affect* (happy, sad, angry, frightened) was the within-subject factor and *group* (RHD, LHD, NHD) was the between-subject factor. Results revealed a significant main effect for group [F(2,33) = 8.16, $P < 0.001$], which merely reflected the findings of the previous analysis that the RHD group performed more poorly on the emotional imagery task than did the LHD and NHD groups. A main effect for *type affect* was also observed [F(3,96) = 5.87, $P < 0.01$], and indicated that imaging angry expressions was more difficult than imaging happy, sad or frightened expressions. This pattern was present to the same extent across all groups [i.e. non-significant Group×Type affect interaction, F(6,96) = 0.37, $P = 0.89$], thereby providing no support for differential hemispheric involvement in imaging positive versus negative emotional facial expressions.

Perceptual tasks. The data from the two facial perceptual tasks (affect judgements, identity judgements) were also analysed using repeated measures ANOVA. The within-subject factor was *type facial task* (emotional judgement, identity judgement) and the between-subject factor was *group* (RHD, LHD, NHD). Results revealed a significant main effect for group [F(2,33) = 18.2, $P < 0.0001$]. Overall, the RHD group (72.7%) performed more poorly across both tasks than did the LHD (X = 86.1%) and NHD groups (X = 94.6%, $P < 0.05$). A main effect for task was also found [F(1,33) = 25.51, $P < 0.01$], in that judgements of facial identity were more accurate than judgements of facial emotions (facial identity = 89.0%; facial emotion = 79.9%). Lastly, a significant Task×Group interaction was observed [F(2,33) = 4.9, $P < 0.01$]. *Post hoc* comparisons (Tukey HSD) revealed that the RHD group was worse at discriminating facial affect than was the LHD group, which was in turn worse than the NHD group (RHD = 67.5%, LHD = 78.3%, NHD = 93.8%). Similarly, the RHD group was worse at discriminating neutral faces than were the LHD or NHD controls. The LHD and NHD groups did not differ on this task (RHD = 73.9%, LHD = 93.8%, NHD = 94.8%). Both the RHD and LHD groups performed worse when making affect judgements than when making identity judgements, and the NHD group performed comparably across the affect and identity judgement tasks.

Individual case data

The results of the previous analyses indicated that RHD patients, as a group, were more impaired on the emotion than object imagery tasks (and vice versa for the LHD group). Similarly, RHD patients were also more impaired on perceptual tasks involving facial emotion than was the LHD group. Although important in its own right, these group findings do not provide the type of information that would enable one to make inferences about status of the hypothetical 'facial emotion lexicon'. Thus, the purpose here was to examine the performance of individual patients on a case-by-case basis. The reason for doing so was to determine whether different patterns of deficits would emerge across the emotional imagery and perceptual tasks and whether they corresponded to damage of specific neuroanatomic regions. That is, would some RHD patients display an isolated defect on the facial emotion imagery task, yet perform normally on object imagery and perceptual tasks? Would others be impaired on all tasks involving facial emotions (both perceptual and imagery), with sparing of non-emotional tasks (object imagery, identity discrimination)? Such results would suggest the existence of some form of facial affect agnosia. Alternatively, would others display marked defects on the perceptual tasks (both emotional and neutral), yet perform normally on imagery tasks?

To determine this, 0.01 confidence intervals were constructed around the mean performance of the NHD control group across the four experimental tasks. Scores of individual LHD and RHD patients that fell below the 0.01 confidence interval of the control group were considered impaired. The 'cut-offs' obtained from the NHD group for each of the experimental tasks were as follows: Facial Emotion Imagery = 83.1% (X = 91.8%, SD = 3.2); Object Imagery = 67.7% (X = 89.6%, SD = 8); Facial Emotion Perception = 76.4% (X = 93.8%, SD = 6.4); and Facial Identity Perception = 80.7% (X = 95.4%, SD = 5.4).

As can be seen in Fig. 3, the behavioural performance of the patients was quite heterogeneous, and several different 'patterns' were observed in the RHD and LHD groups. Specifically, one subtype consisted of four individuals with a facial affect agnosia (*see* Fig. 3, subtype 1). They were selectively impaired on imaging facial emotions and in identifying visible emotional faces, both presumably stemming from disruption of the facial emotion lexicon. Three RHD patients and one LHD patient displayed this pattern. A second subtype consisted of individuals who appeared to have visuoperceptual disturbance in conjunction with a facial affect agnosia (*see* Fig. 3, subtype 2). This was observed in four RHD patients, who performed normally on the object imagery task, but were impaired on emotional imagery and the two perceptual tasks (facial affect, facial identity). A third subtype consisted of three individuals who appeared to have a selective imagery defect (*see* Fig. 3, subtype 3). These patients performed normally on perceptual tasks involving facial affect and facial identity, but were impaired on imagery tasks. This subtype could be further delineated on the basis of the content of the imagery tasks. Two patients, both with LHD, were impaired on both imagery tasks (faces, objects) and thus appeared to have a general imagery generation defect. The remaining individual, who was the only patient in the RHD group whose lesion involved the right inferior occipito-temporal region, had an imagery defect that was specific for emotional faces. He performed normally on perceptual tasks involving neutral and affective faces, and likewise on the object imagery task. His only defect was in imaging facial emotions. A fourth subtype consisted of one RHD patient who performed normally on both imagery tasks (object and emotional faces), but performed at chance level on both perceptual tasks (facial affect, facial identity) (*see* Fig. 3, subtype 4). This patient had a left homonymous hemianopia, with normal visual acuity in his right visual half field. Although he was not formally tested on low level visual tasks (i.e. contrast sensitivity, texture discrimination), he did not display any clinical features that suggested the presence of an apperceptive agnosia, and he had no difficulty in reading, naming objects or identifying familiar faces. Nevertheless, he displayed a high level of visuoperceptual disturbance in discriminating unfamiliar faces and facial affect, with preservation of imagery abilities. This pattern was not observed in any of the LHD patients. A fifth subtype was globally impaired across all imagery and perceptual tasks that were given (*see* Fig. 3, subtype 5). Included in this group were one RHD patient and one LHD patient. The sixth, and final subtype consisted of six patients (one RHD, five LHD) who performed normally across all perceptual and imagery tasks (*see* Fig. 3,

	Imagery tasks		*Perceptual tasks*			
Defect subtype	*Emotion faces*	*objects*	*Emotion faces*	*Neutral faces*	*No. of subjects with this defect*	
Cutoffs*:	83.1	67.7	76.4	80.7	RHD	LHD
1. Facial affect agnosia	↓ (72–80)#	– (77–82)	↓ (55–70)	– (90–95)	3	1
2. Facial affect agnosia + perceptual defect	↓ (66–77)	– (73–86)	↓ (50–75)	↓ (60–75)	4	0
3. Imagery defects a. Emotional imagery	↓ (53)	– (82)	– (80)	– (85)	1	0
b. Global imagery	↓ (72–80)	↓ (64–64)	– (80–85)	– (90–100)	0	2
4. Perceptual defect	– (88)	– (88)	↓ (55)	↓ (50)	1	0
5. Global defects	↓ (40–63)	↓ (55–64)	↓ (55–70)	↓ (65–80)	1	1
6. Normal	– (86–97)	– (76–91)	– (80–95)	– (85–100)	2	5
7. Other: (a)	– (88–)	↓ (55–63)	↓ (55–75)	– (90–95)	0	2
(b)	– (88)	– (91)	↓ (75)	– (100)	0	1

FIG. 3. Patterns of performance of RHD and LHD patients across imagery and perceptual tasks *Cut-off score based on $P < 0.01$ confidence intervals derived from $\bar{X}$ performance of the NHD group, i.e. $\bar{X} \pm SD \times t$ (1/2 α), where $\alpha = 0.01$. # Numbers in parentheses reflect range of scores that were obtained by subjects in this subgroup. ↓ Performance, impaired and falls below 0.01 confidence interval of control group.

subtype 6). In addition, there were three other LHD patients who showed other performance patterns that were not easily interpretable (e.g. impaired object imagery and impaired facial affect perception) (*see* Fig. 3, subtype 7).

The frequency distribution of RHD and LHD patients displaying the various subtype patterns described above is also depicted in Fig. 3. The low number of subjects in conjunction with the large number of empty 'cells' precluded formal statistical analyses (i.e. chi-square).

DISCUSSION

In the present study, RHD and LHD patients as a group showed opposite patterns of performance on two visual imagery tasks; one involved imagery for facial emotions and the other involved imagery for common objects, people and animals. Specifically, the RHD group was more impaired on the facial emotion imagery task than on the object imagery task, whereas the LHD group showed the opposite effect. In discussing these findings, an initial starting point is that the RHD group's defective imagery for facial emotions does not reflect a global disturbance in performing imagery tasks *per se*. Although RHD patients were, in fact, impaired on both emotional and object imagery, they were asymmetrically disrupted. Their emotional imagery performance was significantly worse than their object imagery performance. Similarly, no evidence of a global imagery disturbance was seen in the LHD group. As a group, these subjects were impaired only on the object imagery task, and not on the emotional faces imagery task.

Did defects in imaging facial emotions always co-occur with defects in making judgement about visible affective faces (e.g. perceptual tasks)? The answer to this is yes and no. As a group, the RHD patients were impaired at judging whether two facial affects were the same or different. They were also impaired, but to a lesser extent, in judging whether two faces were the same or different persons. Thus, in a general sense the poor performance of the RHD group on the affect imagery tasks does correspond to poor performance on perceptual tasks involving emotional faces and person identity. The 'no' part of this question is that when we examined the patterns of performance of individual RHD patients across the various imagery and perceptual tasks, dissociations were seen and several 'subtypes' emerged from our RHD group. Of particular relevance was one RHD patient with a right inferior occipito-temporal lesion. This individual had a content-specific imagery defect for facial emotions and performed normally on perceptual tasks. Conversely, the opposite was also seen in another RHD patient who failed visuoperceptual tasks involving facial emotions or facial identity, yet performed normally when required to image either facial emotions or objects. Thus, the data from individual cases do indicate that imaging facial emotions can be dissociable from the perception of facial emotions, and dissociations can occur in either direction (impaired imagery with intact perception and vice versa).

Taken together, these findings suggest, at the most general level, that there are hemispheric-specific effects on imagery task performance and that these effects are crucially linked to the type of material that is being imaged. Facial emotion, which was examined in the present study, appears to be one type of stimulus content that can induce these hemispheric effects on imagery performance, although others may exist as well (Goldenberg *et al.*, 1989*a*,*b*). Furthermore, the finding that facial emotional imagery was disrupted by right, but not by left hemisphere lesions is consistent with and supports our view that the right hemisphere may contain a lexicon/representation of facial emotions or at least the hardware for activating these representations. This view hinges, of course, on whether specific neural networks exist for coding facial affect social signals. Some support for this derives from studies measuring single cell recordings in both monkey and man. Investigators from Rolls' laboratory have identified visual neurons in the temporal cortex and amygdala of monkeys that respond selectively to faces and facial expressions (Perrett *et al.*, 1984; Baylis *et al.*, 1985; Leonard *et al.*, 1985). Similar findings have been obtained during intraoperative recordings of awake humans while undergoing epilepsy surgery (Fried *et al.*, 1982; Heit *et al.*, 1988).

There are several mechanisms that might underlie the asymmetrically impaired facial emotion imagery performance of the RHD patients. In discussing these possibilities, we make several assumptions, the first being that the right hemisphere contains a lexicon of facial emotions. The second, taken from Kosslyn (1980, 1987), is that imaging involves a process by which the LTM structural characteristics of events (i.e. facial emotions) are activated and spatially arranged in a short-term visual buffer. Failure of RHD patients on the emotional imagery task could thus occur at several levels. First, the facial emotion lexicon itself might be disrupted or destroyed in certain RHD patients. Individuals in this situation would be unable to image facial emotions. These patients would also be unable to identify visible facial emotions, since the underlying representations are destroyed. Thus, a facial emotion imagery defect would co-exist with and be secondary to a facial affect agnosia. Three of the 12 RHD patients (and one LHD patient) displayed a pure facial affect agnosia.

Secondly, impaired facial emotion imagery could also occur when the process for transcoding the emotion representations into a short-term visual buffer is compromised. This would be a pure imagery generation defect, but one that was specific for emotional faces. Patients with this defect would fail facial emotion imagery tasks, but have no difficulty in identifying visible affective faces. Only one individual displayed evidence of a pure imagery generation defect for facial emotions. This patient had a right inferior occipito-temporal lesion.

Thirdly, failure on facial emotion imagery tasks by RHD patients might also occur when the ability to maintain the 'image' in the buffer was diminished, akin to a defect in short-term visual memory. The tasks used in the present study do not enable us to address this possibility or to distinguish it from a defect in imagery generation *per se*.

Fourthly, impaired performance on the facial emotion imagery task by RHD patients might also arise from deficits in analysing the structural features of the 'imaged' emotional face. In essence this would amount to some sort of defect in the visuospatial operations that act on the imaged event. These patients would be able to generate images of facial emotion, but would then be unable to perform necessary spatial analyses of the imaged face in order to answer questions about its structural characteristics. One would also assume, for the sake of parsimony, that defective visuospatial operations should also compromise the analysis of visible faces (either emotional or neutral). Thus, individuals in this situation should perform poorly on the facial imagery task and on both facial perceptual tasks. Four RHD patients (and no LHD subjects) showed this pattern. The problem that arises here relates to the assumption, commonly made by imagery theorists, that the various spatial operations involved in analysing imaged events are identical in format to those used in analysing visible events. If this is the case, then it becomes difficult to explain the performance of one RHD patient who was dramatically impaired on both perceptual facial tasks, but performed normally in both imagery tasks. Operations for analysing imaged events would appear to be intact, while operations for analysing visual input would appear to be disrupted. To account for this pattern, one could invoke an explanation along the lines of intact visuospatial analysers that have been disconnected from perceptual events but not from imaged events. Alternatively, somewhat different processes may be involved in analysing visual input versus imaged events.

Finally, failure on facial emotion imagery tasks by RHD patients could also result from a visual-verbal disconnection. In this situation, verbal semantics (i.e. the instruction to image a sad face) would not have access to the facial emotion representations. The ability of such patients to image facial emotions should be intact, although they would do poorly when verbally instructed to image facial emotions due to their visual-verbal disconnection. No difficulty should arise when they are asked to image a facial emotion that corresponds to another non-verbal signal (i.e. emotional prosody). For example, if presented an emotionally intoned sentence and asked to image the facial emotion corresponding to the tone of voice of the speaker, patients with visual-verbal disconnection should perform normally. This should occur because the facial emotion representations have been accessed by other than a verbal route. Although two cases of facial affect anomia following RHD have been previously described in the literature (Bowers and Heilman, 1984; Rapcsak *et al.*, 1989), in neither of these cases was imagery for facial emotions assessed, either verbally or via other non-verbal signals of emotion. Unfortunately, no cases of visual-verbal disconnection were observed in the current sample of RHD patients that would enable us to test their imagery performance. [All subjects who participated in this study were given the Florida Affect Battery-Revised (Bowers *et al.*, 1989), which includes tasks specifically designed to assess for the presence of a visual-verbal disconnection. Specifically, these include tests of facial affect naming and selection of named facial prototypes, e.g. 'point to the angry face'. The complete results of this battery are described elsewhere by Blonder *et al.* (1991).] Consequently, one cannot attribute impaired imagery for facial emotion in any of the RHD patients to a visual-verbal disconnection (i.e. facial affect anomia).

Although it appears from our results that the inability to image facial emotions and to identify visible facial emotions is associated with a lesion of the right hemisphere, we do not know whether each of the behavioural subtypes, discussed above, has a unique neuroanatomic locus. We performed a preliminary examination of the CT/MRI scans of our patients using the template-gyral checklist method. No obvious patterns were apparent, with the exception of the patient having the pure facial emotion imagery defect, whose lesion was confined to the right inferior occipito-temporal region. However, correlations between behavioural abnormalities and lesion sites require a much larger number of subjects than were examined in this study.

Lastly, although our findings suggest that the right hemisphere plays a critical role in imaging facial emotions, it is necessary to temper our interpretations in the light of several methodological issues inherent in our study. One issue concerns the assumption that patients actually used visual imagery to answer questions about the structural characteristics of facial emotions during the facial emotion imagery task. It is of course possible that subjects relied on general semantic knowledge about facial expressions, i.e. knowledge that upturning lips are associated with a smiling, happy facial expression. This is of less concern for the object imagery task, which was derived from the empirically tested high-imagery items of Eddy and Glass (1981). When developing questions for the facial emotion imagery task, we were aware of this problem and attempted to use items that minimized reliance on semantic knowledge and maximized the possibility that subjects would have to visually image the facial emotions. We have no empirical proof on this matter other than the imagery ratings that were obtained from college students who judged the extent they relied on visual imagery to answer the emotion imagery items. Although these subjects indicated that they visually imaged the emotional faces while answering specific questions (mean imagery rating = 4.75 on a 5-point rating scale), it is nevertheless difficult to know the 'true state' of affairs or processes that were actually being used based on verbal report alone.

A second, related issue concerning the facial emotion imagery task is the extent to which subjects actually portrayed the facial emotion themselves and answered questions based on proprioceptive facial feedback cues. Only one patient was actually observed to do this, and stopped when instructed to discontinue this strategy. Since facial electromyogram measurements were not obtained during the facial imagery task, we cannot definitively rule out that covert muscular contractions were made and used as cues.

A third issue is that the facial imagery and object imagery tasks were not identical in format. Our rationale was to include at least one task that had previously been shown (experimentally) to rely on high imagery. These were the object imagery items taken from Eddy and Glass (1981), which consisted of three types of questions, including (*a*) 2-choice decisions, e.g. 'Is the date on a penny toward the top or the bottom?' (12 items); (*b*) responsive naming, e.g. 'What number from 1 to 10 does a peanut look like?' (6 items); and (*c*) yes/no responses, e.g. 'Is the giraffe's neck longer than its tail?' (6 items). In contrast, all the items of the facial imagery task required yes/no responses.

Although the object imagery and facial imagery tasks were comparable in terms of overall difficulty level (based on the performance of the normal controls), the question arises whether the different task formats might be more responsible for the observed hemispheric differences in imagery performance than the contents of the imagery tasks *per se* (objects versus facial emotions). In other words, the right hemisphere might be more adept at making yes/no responses, whereas the left hemisphere might be better at responsive naming and 2-choice decisions. To address this possibility, *post hoc* analyses were conducted in which we examined the frequency of errors made by the RHD and LHD patients across the 3 different formats of the object imagery task. The distribution of errors across the 2-choice, yes/no and responsive naming items was 43%, 10.4% and 46% for the RHD group versus 49%, 13.8% and 37% for the LHD group. These distributions were not significantly different ($\chi^2 = 0.12$, $P > 0.05$). Taken together, these findings suggest that the different formats of the object and facial imagery tasks did not differentially impact the imagery performance of the RHD and LHD patients. In other words, the hemispheric differences that occurred in imaging objects versus facial emotions were not due to how the imagery questions were framed, in terms of yes/no decisions, responsive naming, or 2-choice alternatives.

A final concern relates to the 'multiplicity' of behavioural subtypes that were identified in our study. These occurred in the context of a relatively small sample of brain impaired subjects (n = 24). Although these subtypes 'made sense' from the theoretical perspective that we adopted, the possibility nevertheless remains that these subtypes were artefactual and due to statistical aberration. Future studies using larger patient populations are needed to further address the validity of these subtypes.

Implications for hemispheric mediation of imagery

Current controversy exists regarding the hemispheric mediation of visual imagery (for reviews, *see* Ehrlichman and Barrett, 1983; Kosslyn, 1987; Sergent, 1990). Some have argued that the left hemisphere is solely responsible for placing LTM representations into the visual buffer (Farah, 1984). This argument has been supported by findings with a split brain patient (Kosslyn *et al.*, 1985), a laterality study with normals (Farah, 1986) and a retrospective review of clinical cases reported in the literature (Farah, 1984). Others, however, have found evidence for a right hemisphere superiority for visual imagery (Corballis and Sergent, 1988; Sergent, 1989).

The difficulty in accepting a view that it is only the left hemisphere (or only the right hemisphere) that houses imagery is that it does not make sense, from a neural network perspective, that the processes that underlie imagery generation should be anatomically disparate from the events to be imaged. For example, what advantage would result from having a facial emotion lexicon primarily represented in one hemisphere and a process for activating and transcoding these representations into a visual image located in the other hemisphere? It is much more parsimonious that the processes underlying imagery generation should be tightly coupled to the neural networks involved in the representations of the events. A similar argument has been proffered by Sergent (1990) in a recent review article.

The alternative view is that both hemispheres may be involved in imagery generation (Ehrlichman and Barrett, 1983; Kosslyn, 1987; Sergent, 1990), although hemispheric asymmetries arise when the LTM representations of events to be imaged are differentially represented in the hemispheres. As such, if the right hemisphere does contain a lexicon of facial emotions, as we have proposed, then one would expect patients with RHD to perform poorly on tasks that required them to access this lexicon in order to 'image' emotional faces. In other words, RHD patients should be impaired in their imagery for emotional faces relative to LHD patients. The findings from our study clearly support this view and further suggest that imagery processes are not solely the province of the left hemisphere or the right hemisphere. Rather, both hemispheres may be involved.

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REFERENCES

BAYLIS GC, ROLLS ET, LEONARD CM (1985) Selectivity between faces in the responses of a population of neurons in the cortex in the superior temporal sulcus of the monkey. *Brain Research, Amsterdam,* **342,** 91–102.

BLONDER L, BOWERS D, HEILMAN K (1991) The role of the right hemisphere in emotional communication *Brain,* **114,** 1115–1127.

BOWERS D, HEILMAN KM (1984) Dissociation between the processing of affective and nonaffective faces: a case study. *Journal of Clinical Neuropsychology,* **6,** 367–379.

Bowers D, Bauer RM, Coslett HB, Heilman KM (1985) Processing of faces by patients with unilateral hemisphere lesions: I. Dissociation between judgments of facial affect and facial identity. *Brain and Cognition*, **4**, 258–272.

Bowers D, Blonder LX, Heilman K (1989) *The Florida Affect Battery-Revised.* Center for Neuropsychological Studies. Gainesville, FL: University of Florida.

Caramazza A (1986) On drawing inferences about the structure of normal cognitive systems from the analysis of patterns of impaired performance: the case for single-patient studies. *Brain and Cognition*, **5**, 41–66.

Corballis MC, Sergent J (1988) Imagery in a commissurotomized patient. *Neuropsychologia*, **26**, 13–26.

DeKosky ST, Heilman KM, Bowers D, Valenstein E (1980) Recognition and discrimination of emotional faces and pictures. *Brain and Language*, **9**, 209–214.

Eddy JK, Glass AL (1981) Reading and listening to high and low imagery sentences. *Journal of Verbal Learning and Verbal Behavior*, **20**, 333–345.

Ehrlichman H, Barrett J (1983) Right hemispheric specialization for mental imagery. a review of the evidence. *Brain and Cognition*, **2**, 55–76.

Ellis AW, Young AW (1988) *Human Cognitive Neuropsychology.* Hove: Lawrence Erlbaum.

Etcoff N (1989) Asymmetries in recognition of emotion. In: *Handbook of Neuropsychology: Emotional Behavior and Its Disorders*, Volume 3, Section 6. Edited by F. Boller and J. Grafman. New York: Elsevier, pp. 363–382.

Farah MJ (1984) The neurological basis of mental imagery: a componential analysis. *Cognition*, **18**, 245–272.

Farah MJ (1986) The laterality of mental image generation: a test with normal subjects. *Neuropsychologia*, **24**, 541–551.

Fried I, Mateer C, Ojemann G, Wohns R, Fedio P (1982) Organization of visuospatial functions in human cortex: evidence from electrical stimulation. *Brain*, **105**, 349–371.

Goldenberg G, Podreka I, Steiner M, Willmes K, Suess E, Deecke L (1989*a*) Regional cerebral blood flow patterns in visual imagery. *Neuropsychologia*, **27**, 641–664.

Goldenberg G, Podreka I, Uhl F, Steiner M, Willmes K, Deecke L (1989*b*) Cerebral correlates of imagining colours, faces and a map—I. SPECT of regional cerebral blood flow. *Neuropsychologia*, **27**, 1315–1328.

Goodglass H, Kaplan E, Weintraub, S (1983) *The Boston Naming Test.* Philadelphia: Lea and Febiger.

Heilman K, Bowers D (1990) Neuropsychological studies of emotional changes induced by right and left hemisphere lesions. In: *Psychological and Biological Approaches to Emotion.* Edited by N. Stein, B. Leventhal and T. Trabasso. New York: Lawrence Erlbaum, pp. 97–114.

Heit G, Smith ME, Halgren E (1988) Neural encoding of individual words and faces by the human hippocampus and amygdala. *Nature, London*, **333**, 773–775.

Kertesz A (1982) *Western Aphasia Battery Test Manual.* New York: Grune and Stratton.

Kosslyn SM (1980) *Image and Mind.* Cambridge, MA: Harvard University Press

Kosslyn SM (1987) Seeing and imaging in the cerebral hemispheres: a computational approach. *Psychological Review*, **94**, 148–175.

Kosslyn SM, Holtzman JD, Farah MT, Gazzaniga MS (1985) A computational analysis of mental image generation· evidence from functional dissociations in split-brain patients. *Journal of Experimental Psychology: General*, **114**, 311–341.

Leonard CM, Rolls ET, Wilson FA, Baylis GC (1985) Neurons in the amygdala of the monkey with responses selective for faces. *Behavioural Brain Research*, **15**, 159–176.

Ley RG, Bryden MP (1979) Hemispheric differences in processing emotions and faces. *Brain and Language*, **7**, 127–138.

Perrett DI, Smith PAJ, Potter DD, Mistlin AJ, Head AS, Milner AD *et al.* (1984) Neurons responsive to faces in the temporal cortex: studies of functional organization, sensitivity to identity and relation to perception. *Human Neurobiology*, **3**, 197–208.

Rapcsak SZ, Kasniak AW, Rubens AB (1989) Anomia for facial expressions: evidence for a category specific visual-verbal disconnection syndrome. *Neuropsychologia*, **27**, 1031–1041.

Semenza C, Bisiacchi P, Rosenthal V (1988) A function for cognitive neuropsychology. In· *Perspectives on Cognitive Neuropsychology.* Edited by G. Denes, C Semenza and P. Bisiacchi. Hove: Lawrence Erlbaum, pp. 3–30.

SERGENT J (1989) Image generation and processing of generated images in the cerebal hemispheres. *Journal of Experimental Psychology. Human Perception and Performance,* **15,** 170–178.

SERGENT J (1990) The neuropsychology of visual image generation: data, method, and theory. *Brain and Cognition,* **13,** 98–129.

SHALLICE T (1988) *From Neuropsychology to Mental Structure.* Cambridge: Cambridge University Press.

UHL F, GOLDENBERG G, LANG W, LINDINGER G, STEINER M, DEECKE L (1990) Cerebral correlates of imagining colours, faces and a map—II. Negative cortical DC potentials. *Neuropsychologia,* **28,** 81–93.

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AMNESIA IN MAN FOLLOWING TRANSECTION OF THE FORNIX

A REVIEW

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SUMMARY

Published accounts of the effects of fornix damage on memory in man are critically evaluated. Most weight is given to cases of surgical transection of the fornix, though other causes of fornix damage are briefly discussed. It is concluded that fornix transection causes amnesia.

INTRODUCTION

The role of the fornix in memory is of central importance in understanding the functional basis of amnesia. There is ample modern evidence that amnesia is often associated with damage to either the hippocampus (Cummings *et al.*, 1984; Zola-Morgan *et al.*, 1986) or the mamillary bodies (Mair *et al.*, 1979; Dusoir *et al.*, 1990). The fornix provides a powerful connection between these two structures, projecting from the subiculum of the hippocampus to the medial mamillary nuclei (Swanson and Cowan, 1975). Delay and Brion (1969) put forward the hypothesis that a single functional pathway subserving memory runs from the hippocampus through the fornix to the mamillary bodies, and that the same functional consequence, namely amnesia, results from interruption of this pathway at any of its stages. To assess the adequacy of this hypothesis, the effects of direct damage to the fornix must be established. Experimental studies in rhesus monkeys have shown that surgical transection of the fornix produces memory impairments analogous to those of human amnesic patients (Gaffan, 1991*a,b*). In man, circumscribed lesions of the fornix are uncommon but the available reports on the effects of such lesions on memory clearly deserve careful study, even though the older of these reports are often lacking in detail. Since we know of no existing secondary source which adequately assesses this evidence, we present here a brief review of it.

Amnesia has often been attributed to fornix damage in patients with tumours (by Rudge and Warrington, 1991, for example), wounds (Grafman *et al.*, 1985), vascular accidents (Brion *et al.*, 1969) or other degenerative processes (Grünthal, 1964). Because of the widespread damage additional to fornix lesions in such cases, this evidence is not so conclusive as the evidence from discrete surgical transection of the fornix, which we review in detail below; nonetheless, it is clearly consistent with Delay and Brion's hypothesis. However, in a patient described by Woolsey and Nelson (1975), destruction

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of the fornix by a tumour was reported to have had no effect on memory. Woolsey and Nelson found at autopsy that a tumour had destroyed 80% of the fornix bilaterally in a patient who, according to his sister, had shown no memory impairment. This observation cannot be taken as conclusive, however, since the patient had rapidly growing tumours and was in a state of profound mental confusion, or worse, for the last 10–14 days of his life; much of the fornix damage observed at autopsy may therefore have been produced at a time when not even the most informal assessment of memory could have been made. Thus, the evidence from patients with widespread lesions involving the fornix is consistent with the hypothesis that fornix damage produces amnesia, but is not conclusive. We turn now to the evidence from patients with surgical transection of the fornix.

A number of patients with intractable temporal lobe epilepsy have been operated upon to transect the fornix unilaterally or bilaterally. The rationale for this surgery, first put forward by García Bengochea *et al.* (1954), was to interrupt the spread of epileptic activity through the fornix from the hippocampus in patients thought to have a primary site of epileptic discharge in the hippocampus. This procedure appears to be no longer carried out, however, since the effects on epilepsy were on the whole disappointing (Sonnen *et al.*, 1976; Marossero *et al.*, 1980). In assessing the reported effects on memory in this patient group the difference between unilateral and bilateral transection is crucial. Łuczywek and Mempel (1980) and Oxbury and Oxbury (1989) have shown that, in patients with a diseased epileptogenic hippocampus, unilateral ablation of the hippocampus itself does not impair memory by comparison with the patient's own pre-operative ability and can, if it alleviates epilepsy, even improve it; furthermore, the pre-operative memory ability of such patients is poorer than normal. These effects are understandable functionally, since epileptogenic hippocampal tissue shows morphological abnormalities which suggest that its normal function is severely impaired while cells are still alive and capable of generating epileptic discharge (Scheibel *et al.*, 1974). Unilateral transection of a fornical column which projects from a hippocampus in this diseased state should equally be expected not to produce a memory impairment. Bilateral transection of the fornix in such patients, on the other hand, should be expected to impair memory, according to Delay and Brion's hypothesis, since this procedure will affect the output of the normal hippocampus in the other hemisphere. As is well known, a bilateral ablation including the hippocampus itself in a single epileptic patient produced such a severe memory disorder that the procedure was not repeated for the alleviation of epilepsy in spite of its success in this regard (Scoville and Milner, 1957).

Surgical transection of the fornix has also sometimes been necessary in the course of removing a colloid cyst from the third ventricle. These patients must be considered separately from the epileptic patients. Colloid cysts always originate in the taenia choroidea at the interventricular foramen, rather than in nervous tissue (Nitta and Symon, 1985), and there is therefore no reason to suspect neural pathology in the hippocampus in these patients. Thus, there are no grounds for expecting unilateral fornix damage to be without effect on memory in these patients (unlike the epileptic patients), although on general grounds one might expect the efffect of a unilateral transection to be less severe than that of a bilateral transection.

Thus the functional effects relevant to the Delay-Brion hypothesis concern memory disorder following bilateral fornix transection in patients with temporal lobe epilepsy, and memory disorder following either unilateral or bilateral fornix transection in colloid cyst patients. These are reviewed in turn below. We begin with the colloid cyst patients, since they present the clearer picture.

FORNIX DAMAGE IN THE REMOVAL OF COLLOID CYSTS

Colloid cysts need to be removed from the third ventricle immediately inferior to the fornix, and this removal is accomplished surgically by an approach into the lateral ventricle either through the corpus callosum or through the frontal lobe. In order to remove the cyst the surgeon may then sometimes have to sacrifice the fornix either unilaterally or bilaterally. Two descriptions of single cases (Sweet *et al.*, 1959; Christiansen, 1971) have reported that the surgeon intentionally transected the fornix bilaterally in order to gain access to the cyst. Both of the patients had severe memory disorder as a result of this procedure. Cameron and Archibald (1981) reported severe memory impairment following intentional transection of the left fornix in removal of a colloid cyst, also in a single case. Carmel (1985) described 2 patients in whom the surgeon intentionally transected the right fornix. Again, a severe memory impairment was observed in these patients. Equally important evidence indicates that removal of a colloid cyst does not of itself entail memory disorder, if the fornix is not damaged. Carmel (1985) observed no memory impairment in a large series of patients in whom fornix section had not been necessary in removing the cyst. Nitta and Symon (1985) reported that in 36 cases they had never found it necessary to transect either of the columns of the fornix, and that the surgical procedure did not produce memory disorder in any of these patients.

This evidence was recently further strengthened in a study by Gaffan *et al.* (1991). They used magnetic resonance imaging to demonstrate that 2 patients who had become amnesic as a result of an operation to remove a colloid cyst did indeed, as suspected, have fornix damage. The scans further confirmed that no other damage was visible except for the incision in the corpus callosum. Furthermore, the memory impairments of these 2 patients were documented by formal psychological tests (Gaffan *et al.*, 1991; Hodges and Carpenter, 1991).

Memory deficit following colloid cyst removal was also attributed to fornix damage by Jeeves *et al.* (1979). The only negative instance comes from a paper by Cairns and Mosberg (1951), one of the most influential of early reports on colloid cyst removal. The patients in this report are described as having no serious memory impairment as a result of surgery. The surgical descriptions make it clear that the fornix was transected in one of the patients in the course of the operation to remove the cyst; it is not clear whether the transection was unilateral or bilateral. No formal memory tests were conducted. Cairns and Mosberg were among the first to establish that a colloid cyst (which is itself an immediately life-threatening condition in the patients from whom it is removed) could be safely removed without life-threatening consequences, and it may have been that a memory impairment seemed unimportant in this context. Furthermore, before the impact of Scoville and Milner's report on hippocampal damage and amnesia in 1957, surgeons will not have been alert to the possibility that fornix transection could cause memory disorder; it is possible that an isolated case of memory disorder was attributed to some other cause.

A report by Dott (1938) has also been cited (by Garcia-Bengochea and Friedman, 1987) as showing that fornix transection in the course of colloid cyst removal does not necessarily result in memory impairment. However, each of the 2 patients described in Dott's report had a large hypophyseal tumour invading the third ventricle, not a colloid cyst. It appears from the detailed description of the operations on these 2 patients that the tumours had destroyed the mamillary nuclei bilaterally, in which case no further memory impairment would be expected from transecting the fornix, according to Delay and Brion's hypothesis. It is not clear whether these 2 patients had memory disorder before surgery, since Dott's account is primarily concerned with their vegetative disorders.

BILATERAL FORNIX TRANSECTION IN PATIENTS WITH TEMPORAL LOBE EPILEPSY

The fullest review of this evidence was presented by Garcia-Bengochea and Friedman (1987). As far as we know, no new reports on this patient population have been published since Garcia-Bengochea and Friedman's review appeared. As explained above, the distinction between unilateral and bilateral fornix transection is crucial for the interpretation of effects on memory in this patient population, since unilateral fornix transection in a hemisphere with a diseased hippocampus should be expected to have no effect on memory; Garcia-Bengochea and Friedman tabulated separately reports of bilateral and unilateral fornix transection. According to their account there were 142 published cases of bilateral fornix transection in epileptic patients, of whom none had shown persistent memory loss. We shall show that this conclusion, the most authoritative yet available, is not so strong as it appears. For each of these patients we need to ask what is the evidence that the fornix was transected bilaterally, and what is the evidence as to the effects on memory. This procedure is not as lengthy as it sounds, however, since many of these 142 patients can be immediately discounted from further consideration in the manner described in the following paragraph.

The 142 patients in question are listed in Table 1 of Garcia-Bengochea and Friedman's review (1987), and come from a total of 9 sources. In alphabetical order, the sources are as follows. (1) Barcia-Salorio and Broseta are said to have described 42 such patients; in fact, these all had unilateral fornicotomies, ipsilateral to the presumed epileptogenic hippocampus (Barcia-Salorio and Broseta, 1976, p. 176). (2) Bouchard is said to have described 50 such patients; in fact, these all had unilateral fornicotomies, and the report contains a full discussion of the criteria for deciding which fornix to section (Bouchard, 1971, p. 61). (3) García Bengochea *et al.* (1954, 1956) are said to have described 18 such cases; this is true. (4) Guiot is said to have described 2 such patients, but no reference is given. (5) Hassler and Riechert are said to have described one such patient. Hassler and Riechert's report (1957) describes the severe amnesia produced by bilateral fornix section in this patient, which can be described as not persistent only in the sense that the patient subsequently died. (6) Marossero *et al.* are said to have described 4 such patients. This report makes no comment on the mental state of these patients or the effects of the surgery, beyond the statement that 'the results have been disappointing' (Marossero *et al.*, 1980, p. 148). (7) Mundinger *et al.* are said to have described 3 such patients; in fact, 2 of these are described as having developed Korsakoff-like memory deficits (Mundinger *et al.*, 1976, p. 178). (8) Sonnen *et al.* are said to have described 3 such patients; in fact these had 'bilateral amygdalectomy and ipsilateral fornicotomy', i.e. ipsilateral to the presumed epileptogenic lesion (Sonnen *et al.*, 1976, p. 216). (9) Sugita *et al.* are said to have described 20 such patients; these were indeed described as not showing memory problems, and the surgical intention had been to produce a bilateral lesion of the fornix (Sugita *et al.*, 1971).

Thus, only two reports (those of García Bengochea *et al.* and of Sugita *et al.*) described patients with intended bilateral fornix lesions as having no memory impairment. The surgical methods in these two reports were very different from one another. Sugita *et al.* made stereotaxically guided heat lesions of the fornix. They describe the difficulty of achieving complete fornix transection by this means. Furthermore, one of their patients came to autopsy and the result (illustrated in Sugita *et al.*, 1971, p. 46) clearly shows that more than half of the fornix was spared. Thus the likelihood is that many or all of Sugita *et al.*'s patients will have had substantial sparing of the fornix. García Bengochea *et al.*, on the other hand, made bilateral fornix transections by open surgery, and the presumption must be therefore that the fornix was indeed transected bilaterally in all of their patients. Thus, García Bengochea *et al.*'s observations are much more critical than those of Sugita *et al.*

Turning now to the evidence that these patients had unimpaired memory, this was based simply on a clinical impression. The full extent of García Bengochea *et al.*'s account (1954, p. 177) of the side-effects of bilateral fornix transection through a transfrontal approach is: 'So far, in none of the 12 surviving cases there has been any unfavorable neurological or psychiatric sequela.' Sugita *et al.*'s is equally brief. These operations were of course performed in an attempt to alleviate the very serious effects of intractable severe epilepsy, and the cognitive effects of the surgery were not the prime concern. Thus, Garcia-Bengochea and Friedman (1987, p. 362) acknowledge that their inferences from the epileptic patients could be open to certain objections, 'especially those concerned with detection and quantification of memory deficits'.

Nonetheless, a lack of formal neuropsychological testing cannot by itself explain the belief of García Bengochea *et al.* that bilateral fornix transection did not lead to memory impairment in their patients. If these patients had been similar to the colloid cyst patients described above, then the patients' memory disorder would have been obvious without formal testing. However, it is by no means necessary to conclude that the evident dissimilarity between these two groups of patients was in their degree of memory impairment. In assessing effects on memory we should not forget that García Bengochea *et al.* (1954) made no claim that these surgeries alleviated behavioural or mental disorders in their patients. As candidates for what Scoville and Milner (1957, p. 11) described as 'frankly experimental' surgery, these patients would have been very ill indeed, not only in terms of the frequency of seizures but also in terms of the neurological and behavioural consequences. Almost all of the papers in the collections by Gillingham *et al.* (1976) and Umbach (1971) allude to the profound emotional and intellectual disorders which longstanding, severe and intractable temporal lobe epilepsy led to in their era, often including psychotic symptoms, mental retardation and uncontrollable aggressiveness. It cannot have been easy to detect clinically a specific memory impairment against this background. Indeed, in García Bengochea *et al.*'s second report on their patients (which is in most other respects simply a republication in Spanish of their first report) the difficulty is specifically acknowledged: 'No se han observado cambios en la memoria, pero éstos eran difíciles de evaluar, ya que la mayor parte de los pacientes presentaban cuadros psicóticos más o menos avanzados' (Changes in memory have not been observed, but these were difficult to evaluate, because the majority of the patients presented more or less advanced psychotic syndromes) (García Bengochea *et al.*, 1956, p. 156). In the same way, the effects of bilateral hippocampal ablation on memory were not at first detected when the ablations were made in an unsuccessful attempt to alleviate schizophrenia; they became obvious only when the ablation produced a dramatic alleviation of epilepsy (Scoville and Milner, 1957). We presume that if bilateral fornix transection had had as beneficial an effect on temporal lobe epilepsy and its consequences as bilateral hippocampal ablation did, its effects on memory would have been obvious to García Bengochea *et al.*.

Clearly, no strong conclusion can be confidently drawn from the available evidence on memory after bilateral fornix transection in epileptic patients. With little verification available of the extent of the lesions, and in the total absence of psychometric data, it is impossible in retrospect to weigh the negative judgement of García Bengochea *et al.* (1954) and Sugita *et al.* (1971) against the positive judgements of Hassler and Riechert (1957) and Mundinger *et al.* (1976). The best that can be said is that of all these reports on fornix transection in epileptic patients, Hassler and Riechert's paper stands out in its detailed and thoughtful consideration of all relevant aspects of the case presented, including the only published verification of a complete bilateral fornix transection in an epileptic patient.

CONCLUSION

We have considered the evidence from surgical transection of the fornix in detail, and we have documented the reasons for giving little weight to the mutually contradictory reports on the effect of this procedure in epileptic patients. Much clearer evidence comes from surgical fornix damage in patients with colloid cyst removal, and this evidence gives strong support to Delay and Brion's hypothesis (1969).

REFERENCES

Barcia-Salorio JL, Broseta J (1976) Stereotactic fornicotomy in temporal epilepsy: indications and long-term results. *Acta Neurochirurgica*, Supplement 23, 167–175.

Bouchard G (1971) Long-term results of stereotaxic fornicotomy and fornicoamygdalotomy in patients with temporal lobe epilepsy showing behavioural disturbances. In: *Special Topics in Stereotaxis: Epilepsy, Disorders of Behaviour, and Autonomic Balance.* Edited by W. Umbach. Stuttgart: Hippokrates, pp. 53–64.

Brion S, Pragier G, Guérin R, Mme Teitgen (1969) Syndrome de Korsakoff par ramollissement bilatéral du fornix. *Revue Neurologique*, **120**, 255–262.

Cairns H, Mosberg WH (1951) Colloid cyst of the third ventricle. *Surgery Gynecology and Obstetrics*, **92**, 545–570

Cameron AS, Archibald YM (1981) Verbal memory deficit after left fornix removal: a case report. *International Journal of Neuroscience*, **12**, 201.

Carmel PW (1985) Tumours of the third ventricle. *Acta Neurochirurgica*, **75**, 136–146.

Christiansen JC (1971) Discussion of paper by K. Sugita *et al.* In: *Special Topics in Stereotaxis: Epilepsy, Disorders of Behaviour, and Autonomic Balance.* Edited by W. Umbach Stuttgart: Hippokrates, p. 51.

Cummings JL, Tomiyasu U, Read S, Benson DF (1984) Anmesia with hippocampal lesions after cardiopulmonary arrest. *Neurology, Cleveland*, **34,** 679–681.

Delay J, Brion S (1969) *Le Syndrome de Korsakoff.* Paris: Masson.

Dott NM (1938) Surgical aspects of the hypothalamus. In: *The Hypothalamus: Morphological, Functional, Clinical and Surgical Aspects.* Edited by W. E. Le Gros Clark, J. Beattie, G. Riddoch and N. M. Dott. Edinburgh: Oliver and Boyd, p. 131.

Dusoir H, Kapur N, Byrnes DP, McKinstry S, Hoare RD (1990) The role of diencephalic pathology in human memory disorder: evidence from a penetrating paranasal brain injury. *Brain,* **113,** 1695–1706.

Gaffan D (1991*a*) The role of the hippocampus-fornix-mammillary system in episodic memory. In: *Neuropsychology of Memory* Second edition. Edited by L. R. Squire and N. Butters. New York: Guilford. In press.

Gaffan D (1991*b*) Spatial organization of episodic memory. *Hippocampus,* **1,** 262–264.

Gaffan EA, Gaffan D, Hodges JR (1991) Amnesia following damage to the left fornix and to other sites: a comparative study. *Brain,* **114,** 1297–1313.

García Bengochea F, de la Torre O, Esquivel O, Vieta R, Fernandez C (1954) The section of the fornix in the surgical treatment of certain epilepsies: a preliminary report. *Transactions of the American Neurological Association,* **79,** 176–178.

García Bengochea F, de la Torre O, Esquivel O, Vieta R, Fernández JC (1956) La sección del fórnix en el tratamiento quirúrgico de ciertas epilepsias: comunicación preliminar. *Acta Neurológica Latinoamericana,* **2,** 153–158.

Garcia-Bengochea F, Friedman WA (1987) Persistent memory loss following section of the anterior fornix in humans: a historical review. *Surgical Neurology,* **27,** 361–364.

Gillingham FJ, Hitchcock ER, Nádvorník P (1976) Stereotactic treatment of epilepsy. *Acta Neurochirurgica,* Supplement 23, 1–281.

Grafman J, Salazar AM, Weingartner H, Vance SC, Ludlow C (1985) Isolated impairment of memory following a penetrating lesion of the fornix cerebri. *Archives of Neurology, Chicago,* **42,** 1162–1168.

Grünthal E (1964) Über einen Fall von Korsakow-Syndrom bei Atrophie des Fornix-Systems. *Psychiatria et Neurologia, Basal,* **148,** 3–12.

Hassler R, Riechert T (1957) Über einen Fall von doppelseitiger Fornicotomie bei sogenannter temporaler Epilepsie. *Acta Neurochirurgica,* **5,** 330–340.

Hodges JR, Carpenter K (1991) Anterograde amnesia with fornix damage following removal of IIIrd ventricle colloid cyst. *Journal of Neurology, Neurosurgery, and Psychiatry,* **54,** 633–638.

Jeeves MA, Simpson DA, Geffen G (1979) Functional consequences of the transcallosal removal of intraventricular tumours. *Journal of Neurology, Neurosurgery, and Psychiatry,* **42,** 134–142.

Łuczywek E, Mempel E (1980) Memory and learning in epileptic patients treated by amygdalotomy and anterior hippocampotomy. *Acta Neurochirurgica,* Supplement 30, 169–175.

Mair WGP, Warrington EK, Weiskrantz L (1979) Memory disorder in Korsakoff's psychosis: a neuropathological and neuropsychological investigation of two cases. *Brain,* **102,** 749–783.

Marossero F, Ravagnati L, Sironi VA, Miserocchi G, Franzini A, Ettorre G *et al.* (1980) Late results of stereotactic radiofrequency lesions in epilepsy. *Acta Neurochirurgica,* Supplement 30, 145–149.

Mundinger F, Becker P. Groebner E, Bachschmid G (1976) Late results of stereotactic surgery of epilepsy predominantly temporal lobe type. *Acta Neurochirurgica,* Supplement 23, 177–182.

Nitta M, Symon L (1985) Colloid cysts of the third ventricle: a review of 36 cases. *Acta Neurochirurgica,* **76,** 99–104.

Oxbury J, Oxbury S (1989) Neuropsychology: memory and hippocampal pathology. In. *The Bridge between Neurology and Psychiatry.* Edited by E. H. Reynolds and M. R. Trimble. Edinburgh: Churchill Livingstone, pp. 135–150.

Rudge P, Warrington EK (1991) Selective impairment of memory and visual perception in splenial tumours. *Brain,* **114,** 349–360.

Scheibel ME, Crandall PH, Scheibel AB (1974) The hippocampal-dentate complex in temporal lobe epilepsy: a Golgi study. *Epilepsia,* **15,** 55–80.

SCOVILLE WB, MILNER B (1957) Loss of recent memory after bilateral hippocampal lesions. *Journal of Neurology, Neurosurgery, and Psychiatry,* **20,** 11–21.

SONNEN AEH, MANEN Jv, DIJK B VAN (1976) Results of amygdalotomy and fornicotomy in temporal lobe epilepsy and behaviour disorders. *Acta Neurochirurgica,* Supplement 23, 215–219.

SUGITA K, DOEI T, MATSUGA N, TAKAOKA Y (1971) Clinical study of fornicotomy for psychomotor epilepsy and behavior disorder. In: *Special Topics in Stereotaxis: Epilepsy, Disorders of Behaviour, and Autonomic Balance.* Edited by W. Umbach. Stuttgart: Hippokrates, pp. 42–52.

SWANSON LW, COWAN WM (1975) Hippocampo-hypothalamic connections: origin in subicular cortex, not Ammon's horn. *Science,* **189,** 303–304.

SWEET WH, TALLAND GA, ERVIN FR (1959) Loss of recent memory following section of fornix. *Transactions of the American Neurological Association,* **84,** 76–82.

UMBACH W (1971) *Special Topics in Stereotaxis: Epilepsy, Disorders of Behaviour, and Autonomic Balance.* Edited by W. Umbach. Stuttgart: Hippokrates.

WOOLSEY RM, NELSON JS (1975) Asymptomatic destruction of the fornix in man. *Archives of Neurology, Chicago,* **32,** 566–568.

ZOLA-MORGAN S, SQUIRE LR, AMARAL DG (1986) Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *Journal of Neuroscience,* **6,** 2950–2967.

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A SPECIFIC DEFICIT FOR NUMBERS IN A CASE OF DENSE ACALCULIA

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SUMMARY

In this study we investigated the acalculic condition of a patient, C.G., with the classical signs of Gerstmann's Syndrome: finger agnosia; right-left disorientation; a profound agraphia (but with an equally profound alexia) and a remarkably dense acalculia. Using a series of number processing and number knowledge tasks, a selective impairment for numbers was demonstrated. Within the category of numbers C.G. showed a largely preserved ability to deal with numbers below 4, in all tasks and in all modalities, while she was totally unable to deal with numbers above 4. The consistency of responses and the ineffectiveness of cueing indicated that numbers above 4 were lost, rather than hard to access. Further testing showed that this impairment did not result from a more general semantic memory problem, a difficulty in understanding quantities or a deficit in reasoning abilities thought to underlie the concept of numbers. Difficulty with some other ordinal structures was also present, but appeared unrelated to those affecting numbers.

INTRODUCTION

Selective sparing of semantic memory routinely occurs in the amnesias (Shallice, 1979), but semantic memory itself can suffer selective deficits affecting a single domain or category of knowledge. In the study reported here, we describe an unusual and highly-circumscribed deficit in knowledge of numbers.

Category-specific deficits

Since Nielsen's (1936) observation of a patient who showed an impairment in identifying inanimate objects, but not in recognizing living things, there have been many reports of selective deficits in particular semantic domains, like body-parts and objects (Yamadori and Albert 1973). More recently, a series of seminal studies by Warrington *et al.* (Shallice and Warrington, 1975; Warrington, 1975; McKenna and Warrington, 1978; Warrington and McCarthy, 1983; Warrington and Shallice, 1984), found clear double dissociations in several distinct knowledge domains: for example, abstract as compared with concrete words (Shallice and Warrington, 1975; Warrington 1975), living things and food as compared with inanimate objects (Ratcliff and Newcombe, 1982; Warrington and McCarthy, 1983, 1987; Warrington and Shallice, 1984; Sartori and Job, 1988; Silveri and Gainotti, 1988). Subsequently, selective difficulties affecting specific semantic domains have frequently been attested: for example, fruits and vegetables (Hart *et al.*, 1985), small manipulable objects (Warrington and McCarthy,

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1987), proper names (McKenna and Warrington, 1978; Semenza and Zettin, 1989) and body parts (Dennis, 1976; Semenza, 1988).

The discovery of impairments to particular semantic categories support the notion that semantic knowledge is far from being functionally homogeneous (Shallice, 1988), suggesting, as McCarthy and Warrington (1988) pointed out, that semantic knowledge is categorical in its organization.

It has further been observed that category-specific deficits may be confined to a particular modality. So, for example, the patient T.O.B. was able to identify plants and animals from pictures, but not from verbal description, while inanimate objects could be identified from both types of presentation (McCarthy and Warrington 1988). Such observations have led to the claim that separate semantic systems must be associated with the verbal and the non-verbal (visual) modalities (Warrington, 1975; Shallice, 1987, 1988). Although this modality-specificity is plausible for picturable objects, it is unclear whether every semantic domain has separate modality-linked representations, since modality effects have yet to be observed for abstract domains, such as abstract words or proper names (Semenza and Zettin, 1989).

Special properties of the domain of number knowledge

Numbers constitute a domain of knowledge that is unusual in several ways. It is not evident that numbers fall into the verbal system. Piaget's (1952) account of the development of the number concept in the child, does not depend on the acquisition of a number vocabulary. Gelman and Gallistel (1978) have argued that learning a stable sequence of verbal labels aids the development of counting skills, though this does not seem to be a necessary requirement for the development of number concepts. Hermelin and O'Connor (1990) report a relevant case of an autistic boy with an apparent total developmental aphasia. He was unable to speak or to understand spoken language. He was unable to obtain a score on the Peabody Picture Vocabulary test, and, although he learned a few elementary Paget-Gorman signs, he never used them spontaneously. Nevertheless, he was able to write and read numerals, to add, subtract, multiply and divide large numbers, and to generate and recognize factors and primes far more quickly than an adult with a mathematics degree. The clear implication of this case, is that verbal abilities are unnecessary for the development of even a high level of number skill. Languages without words for numbers above 2, like several Australian Aboriginal languages, do not prevent their speakers calculating and counting when required, nor rapidly acquiring number words from other languages and the ability to use money (Dixon, 1980, p. 108).

It is not obvious that numbers fall into the visual domain either. Recognizing the cardinal number of a set of elements, or comparing the cardinalities of 2 sets, requires abstracting away from the visual properties of the arrays. The arrays do not have to be visual, they can be auditory or tactile; and there is no evidence that the visually handicapped are particularly impaired in number skills. Indeed, it has been claimed that the ability to abstract numerosity information across modalities is an innate precursor of the number concept, based on the recent finding that infants respond differentially to visual and auditory arrays with the same numerosity as compared with arrays with different numerosities (Starkey *et al.*, 1990).

That the number domain should be a paradigm example of an abstract system, rather than one rooted in either words or images, would be unsurprising to philosophers of mathematics (Russell, 1903). It is unlike other abstract domains, in that basic facts (true numerical expressions) can be generated by rule. As a consequence number facts can be computed by procedures based on rules as well as retrieved from memory. Evidence from tests of simple arithmetic indicate that in the early stages of the development of numerical skills, children rely heavily on procedures; with increasing practice and experience, problems of simple arithmetic are more often retrieved directly from memory (Groen and Parkman, 1972).

If the number domain is abstract, and rule-governed, then there may not be separate meaning systems for the verbal and visual modalities. One test of this would be strict item-specificity across modalities. That is to say, in a case of number deficit, are *exactly* the same numbers failed, or not, whatever the modality? It would seem highly unlikely that brain damage would destroy and spare exactly the same items in 2 neurally separable systems.

Selective impairments of numerical skills

The term 'acalculia', originally introduced by Henschen (1919, 1920), has been used to refer to extremely diverse disorders ranging from the inability to recognize numbers to the inability to do arithmetical calculation. According to Jackson and Warrington (1986), of patients suffering cerebral lesions between 7% and 20%, depending on the criterion, show acalculic symptoms.

Following Henschen, Berger (1926) drew the theoretically important distinction between secondary and primary acalculia. Secondary acalculia results from a disorder to some other cognitive function, such as aphasia, dyslexia, agraphia as well as attentional disorders and dementia. Primary acalculia occurs when the disorder cannot clearly be attributed to other cerebral disturbances. Patients with an inability to interpret the position or directions of numbers have been described (Kleist, 1934; Krapf, 1937), as have patients with faulty memory for tables (Cohn, 1961; Benson and Weir, 1972). Patients have been reported with loss of 'arithmetical procedure' (Grewel, 1969; Benson and Weir, 1972); and also with an inability to identify arithmetical symbols (Ferro and Silveira Botelho, 1980). A further type of calculation disorder, associated with frontal lobe damage, has been described by Luria (1966), in which patients have difficulty with novel problems requiring planning.

These clinical studies did not directly address the issue category specificity of the types described above. More recently, a series of experimental neuropsychological studies by McCloskey *et al.* (*see* McCloskey and Caramazza, 1987, and Caramazza and McCloskey, 1987, for a review) have been primarily concerned with describing the components required to read, write and pronounce numbers. The data have been presented and discussed on the framework of an information processing model similar to those used as a framework for describing reading disorders (e.g. Morton and Patterson, 1987), with separate production and comprehension processing for number words and numerals.

Deloche and Seron (1987 for a review) propose an analysis for 'transcoding' between arabic numerals and number names in terms of the notion of 'stack structures' (Deloche and Seron, 1982*a*,*b*). Stacks are ordered one dimensional arrays: an item belongs to a particular stack and has a specified position within the stack. Patients make 2 types of error: 'stack errors', where the wrong stack (units, teens and tens, etc.) is selected (e.g. 5 for 'fifty'), and 'errors of position in stack structures', where a lexical mistake picks the wrong name from the right stack (e.g. 5 for 'eight'). Deloche and Seron (1984) suggested that the stack concept can be relevant to other ordinal domains, like names of the days in the week, the months in the year, etc. We prefer the term 'ordinal structure', for both numbers and other ordinal domains, since it draws attention to ordering of a set of elements though the types of ordering may be formally distinct. So while the set of integers has proper ordering and no last term, days of the week and months of the year have a cyclic ordering.

The first detailed analysis of acalculic disorders from a cognitive neuropsychological perspective was carried out by Warrington (1982). She reported an acalculic patient, D.R.C., who was able to carry out simple calculations only very slowly, and with frequent errors, despite a clear understanding of arithmetical principles and procedures, and the preservation of knowledge of the cardinal values of numbers. A specific loss of number facts for addition, subtraction and tables was advanced to explain this deficit. Warrington (1982) also briefly reported another patient, S.T.H., whose difficulties with oral arithmetical calculation seemed to be secondary to a more basic failure at the level of number knowledge. Apart from S.T.H., no patient has been reported who showed a category-specific loss of number knowledge which is common to all modalities.

The patient we report here, C.G., following a stroke, showed a dense and lasting acalculia. The most striking feature was an impairment of number knowledge. This turned out to be not just a category-specific deficit, but, remarkably, a strict *subcategory* deficit of a type never previously documented. Numbers up to 4 are relatively well preserved, while numbers above 4 appear to be completely lost.

The aims of the study are to establish as fully as possible the precise nature of the deficit within the framework of category-specific disorders of semantic memory as it applies to the domain of numbers. This means trying to find answers to the following questions: (1) is the disorder one of impaired access to number knowledge or a degradation of stored number knowledge? (2) is the disorder found in all modalities? (3) does the disorder depend on a wider degradation of semantic memory? (4) can the number of disorder be explained in terms of a general difficulty with ordinal structures? (5) can the number disorder be explained in terms of a deeper problem with understanding quantities? (6) can the number disorder be explained in terms of a deeper problem of formal reasoning generally?

METHODS AND RESULTS

Case report

C.G. is a 59-yr-old right-handed woman. She attended school for a total of 13 yrs. Before her illness she dealt with the administrative side of her family hotel. In October 1987, at the age of 56, she suddenly developed a right hemiparesis and language disturbances due to a cerebral vascular accident (CVA) in the territory of the left middle cerebral artery. A NMR scan (20 November 1987) showed an area of hypodensity involving the left fronto-parietal region (*see* Fig. 1). The patient improved over the following days and months, with the complete disappearance of motor impairment. Her aphasic pattern, initially of global type, showed rapid and almost complete recovery. The patient was first seen as an out-patient at the Clinica Neurologica 1 in Padova in March 1989, 15 mths after the stroke. The data reported here were collected between March 1989 and July 1990.

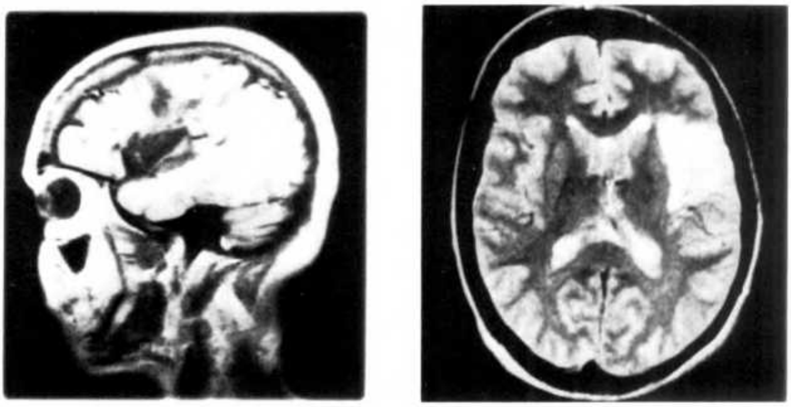

FIG. 1. An MRI scan of patient C.G. showing an area of hypodensity involving the left fronto-parietal region.

Neurological examination

Apart from neuropsychological signs (*see below*), this was entirely within normal limits.

Neuropsychological examination

The patient was oriented in time and place. Her collaboration in testing situation was good and her mood appropriate. She scored 24/36 on the Raven Coloured Progressive Matrices 47. She obtained a verbal IQ of 92, a performance IQ of 108 and a full-scale IQ of 99 on the WAIS. Her pro-rated IQ score and the individual age-scaled scores for each subtest obtained are given in Table 1.

TABLE 1. WAIS INTELLIGENCE QUOTIENTS AND INDIVIDUAL SUBTEST SCORES

Verbal IQ	92
Performance IQ	108
Similarities	13
Vocabulary	9
Picture completion	10
Block design	10
Picture arrangement	8
Arithmetic	0
Digit span	2

A significant selective impairment was observed on the arithmetic and on the digit span subtest of the WAIS where she obtained an age-scaled score of 0 and 2, respectively: C.G. was unable to carry out even the simplest arithmetical problem and could repeat only 2 digits forward, while failing to repeat 2 digits backward. However, if asked to repeat sequences of unrelated words or non-words, she showed a word span for bisyllabic concrete words as well as function words of 4, while here non-word span was 3. Furthermore she scored 4 on the Corsi block tapping test. Table 2 gives a summary of C.G.'s performance on verbal short-term memory tasks.

TABLE 2 REPETITION OF WORDS AND NON-WORDS PERCENTAGE OF FULLY CORRECT LISTS

Length	*Concrete words*	*Function words*	*Non-words*
2	100	100	100
3	100	100	60
4	70	80	0
5	10	0	0

Her severe impairment on numeracy tasks is described in the experimental section below. The patient's performance was within the normal range in long-term memory tests such as a 10-word learning test, a paired associated learning test and a short story learning test (De Renzi *et al.* 1977), as well as in learning a supra-span spatial sequence. Buccofacial and limb praxis were unimpaired, both on verbal command and on imitation. Her drawing ability on copy was normal, while on command it was slightly impaired. No visual, auditory or tactile agnosia was present. A finger agnosia was noted: the patient was no longer able to indicate fingers on verbal command, to name fingers or to identify fingers touched by the examiner. The indication of body parts (except for fingers) was good; however, the patient was no longer able to discriminate left from right on her body or in extra-personal space. The patient attempted an Italian version of the Shallice and Evans (1978) cognitive estimation test: not one of her responses to the numerical items was satisfactory (e.g. What is the average length of a thousand lire note? 'One centimetre').

In summary, the neuropsychological evaluation showed the presence of a finger agnosia, a right-left disorientation and a selective difficulty emerged in tasks requiring her to deal with numbers.

Language examination

The patient was given an Italian version of the BDAE (Goodglass and Kaplan, 1972). Her spontaneous speech was fluent, but mildly dysarthric. Phrase length was normal and information content was proportional to fluency. No anomia, paraphasia or neologisms were present. Her performance on comprehension subtests of the BDAE was flawless, apart for the presence of selective impairment in word discrimination tasks restricted to numbers and letters. On the shortened version of the token test (De Renzi and Faglioni, 1978) she scored 30/36 (performance within normal limits). Repetition of words and of high and low probability sentences were flawless. Naming, apart from letters, numbers and fingers, was normal (*see below*).

Reading and writing. C.G. had been a good reader: before her illness she used to read daily newspapers, novels and books. After her stroke she became severely dyslexic and dysgraphic. Her score in BDAE's reading and writing subtests was 0. She was no longer able to read aloud single letters and words (0 out of 21 and 0 out of 30, respectively), and she failed to spell aloud or write correctly any letters or words (0 out of 21 and 0 out of 30, respectively). Writing on copy appeared preserved. Furthermore, her ability to match single written words to picture was compromised (3 out of 15) as well as her ability to point on verbal command to single written letters or words (2 out of 21 and 1 out of 15, respectively). The patient was not even able to mark written letters presented among other rotated letters and meaningless shapes (Table 3 gives a summary of C.G.'s performance on reading and writing tasks).

TABLE 3 READING AND WRITING PERFORMANCE

	n	*n correct*
Letters	21	0
Words	30	0
Pointing to a letter	21	2
Pointing to words	15	1
Matching words to pictures	15	3
Mark the letter among shapes	20	2
Writing letters	10	0
Writing words	10	0
Copying letters	10	10
Copying words	10	10

Symbol recognition and naming. Given C.G.'s inability to read, write, understand or even recognize words and single letters, we administered a non-alphanumeric symbol naming task to detect the presence of a more general visual processing impairment in dealing with symbols. Her performance on naming commonly used symbols (signs of the zodiac, road signs and the symbols of Italian political parties, punctuation marks and playing cards) was flawless (*see* Table 4).

TABLE 4 NAMING NON-ALPHA-NUMERIC SYMBOLS

	n	*n correct*
Signs of the zodiac	10	10
Road signs	10	10
Political signs	10	9
Punctuation marks	9	9
Playing cards (pictures)	4	4
Arithmetical signs	4	0

However, the patient was unable to name symbols denoting the arithmetical operations, except on the basis of their physical appearance (e.g. +, 'the cross'; −, 'a little line'; x, 'the cross rotated'; :, 'I can see 2 little dots one over the other'). C.G. was also asked to match the spoken arithmetical symbol name to the corresponding written arithmetical sign and to mark the written arithmetical sign presented together with other meaningless shapes. In both tasks her performance was impaired showing that she is unable to recognize written arithmetical signs.

In summary, C.G.'s earlier aphasic symptoms had entirely resolved apart from the residual difficulties in reading and writing.

Numeracy. The patient complained of severe difficulties in dealing with numbers in her everyday life. She was no longer able to read the time, dial a telephone number, recognize money or check change. She could not produce her own age, clothes size, telephone number, the number of her house, the ages of her children and husband, etc. However, she seemed to have some residual knowledge about numbers in general, since when questioned about the functions of numbers, she correctly replied that people need numbers to count things. She also maintained the notion that numbers are infinite. She complained of being unable to carry out calculations. When questioned, she offered the following definitions of the four basic arithmetical operations, she answered as follows: *Addition*: 'I don't know, I heard it before . . . maybe at school . . . now I really don't remember what it means'; *Subtraction*: 'I think it could be a sort of hole that people make in the earth'. In Italian the word subtract (sottrarre) is phonologically similar to the word for bury (sotterrare); *Multiplication*: 'Yes I remember that Jesus has multiplied loaves and fishes . . . but now I don't know what the word multiplication means'; *Division*: 'Oh yes it means for example a military division . . . a group of people that work for the army'.

Her condition appeared stable and the data obtained in test sessions were consistent over one and a half years.

EXPERIMENTAL INVESTIGATION

Tests of number processing

The first series of tasks sought to establish in some detail the limits of C.G.'s ability to produce, recognize and transcode numbers presented in various ways. In particular, they sought to establish whether numbers above 4 are equally difficult in all tasks, or whether an effect of task modality could be detected. The tasks could, in principle, be carried out if the patient had preserved units for recognizing and producing numbers, and the mappings among the units, even though her understanding of number meanings had been lost.

Number production tasks

A set of 50 numeral stimuli were used in reading aloud and writing to dictation tasks: the 10 single digits from 0 to 9; the 10 teen digits from 10 to 19; 10 two-digit numbers (e.g. 25); 10 three-digit numbers (e.g. 142); and 10 four-digit numbers (e.g. 1245). The same numbers were used for each of the following tests.

Reading aloud. The stimuli were each written on a single card and presented to the patient for reading aloud. C.G. was able only to read numbers from 1 to 4: she could not give any answer for numbers above 4 or for the digit 0. We asked the patient to read Roman numerals. She was able to read aloud numbers just up to three (*see* Table 5).

Writing arabic numerals to dictation. Each stimulus was spoken aloud for written response. The patient was no longer able to write even a single number (*see* Table 5).

Reciting number names. C.G. was asked to count forward from a number given orally by the examiner. C.G. was able to count one by one just up to 4. After 4, she said 'La mia matematica finisce qui' (my mathematics stops here). In doing this task, C.G. always used her fingers, and her residual counting ability appeared extremely slow. The same pattern of results was obtained when she was asked to count objects.

TABLE 5 NUMBER PRODUCTION AND RECOGNITION (IN PERCENTAGE CORRECT)

	Numbers 1–4	*Numbers above 4*
Reading aloud	100	0
Writing	0	0
Pointing on spoken request	100	10*
Discrimination from shapes	100	0*

*Most responses were 'Don't know'

Number recognition tasks

The stimuli consisted of the 10 single digits 0 to 9, 5 teen digits, 5 two-digit numbers, 5 three-digit numbers and 5 four-digit numbers.

Pointing to written arabic numerals on spoken request. The stimuli were randomly arranged on three different cards, each containing 10 numbers. The numbers were spoken aloud in a random order by the examiner and C.G. was asked to match the spoken to the written number. She was able to correctly point just to the numbers from 1 to 4 (*see* Table 5).

Discriminating arabic numerals from meaningless shapes. The stimuli were randomly arranged on 3 different cards, each containing 10 numbers and 20 meaningless shapes. The patient was asked to mark all the numbers that she was able to detect, C.G. marked promptly just the numbers from 1 to 4, claiming not to be able to detect any other numeral (*see* Table 5).

Auditory lexical decision. The patient was presented auditorily with 20 spoken triplets, each of which contained a number word, a common concrete word and a non-word. Words and non-words were length matched to number words. The non-words were derived by changing one phoneme of a real word, to give a pronounceable non-word. The number words were the ten numbers from 1 to 10, 5 two-digit numbers (e.g. 'twenty-two') and 5 three-digit numbers (e.g. 'one hundred and forty'). The patient was asked to say which items in each triplet were words. Again C.G. showed a clear dissociation of numbers from 1 to 4 as compared with all the other numbers. Her performance was correct only for the triplets containing the numbers 1 to 4. For all the other triplets, the patient reported the presence of two non-words: the real non-word and the word for the number above 4.

Number word definition. The same set of number word stimuli used in the auditory lexical decision task was given to the patient, whose task was to define these words. Again C.G. was unable to understand the names of numbers above 4. In fact she was able to reply that the number words below 4 'are numbers', but she was no longer able to define correctly any other number. For example, when asked to define the word 'seven' she answered: 'what is it . . . I've never heard this word before'; for 'ten' she replied, 'I don't know . . . is it a word?'. Interestingly in Italian there are a few examples of number words that can have another lexical meaning. For example, 'venti' (20) also means 'winds', or 'quarantotto' (48) also means 'much confusion'. In these cases C.G. was able to give the non-numerical meaning.

Digit span. It is well-established that word repetition span is superior to non-word span. If C.G. really does treat numbers above 4 as non-words, then there should be span differences for stimuli composed of these numbers as compared with stimuli composed of numbers below 4. Two lists of digits were used: a list of digits composed of numbers above 4 and a list of digits below 4. From each list, 10 sequences of either 2, 3 or 4 numbers were generated at random. No number was repeated within a sequence. Auditory presentation was used. C.G. was asked to repeat immediately the items of the presented sequence in the correct order. Table 6 shows C.G.'s performance on this task. Lists of digits composed of numbers below 4 were recalled better than the lists of numbers above 4: since she showed a digit span of 3 for the first type and a span of 2 for the second type.

TABLE 6 DIGIT SPAN (PERCENTAGE OF LISTS CORRECT)

Length	*Numbers 1–4*	*Numbers above 4*
2	90	90
3	80	30
4	50	0

Knowledge of number order

Although C.G. was unable to count or recite numbers above 4, a further test was devised in which elements from the number series were used in an attempt to prompt or cue retrieval of number names. According to the standard account of degraded storage of information, if an item is lost, as opposed to hard to access, then prompting should have no effect. In the following task, number names were used as prompts for the next and/or the previous number in the series.

'What comes next?' Presentation of the number words was auditory. Three different kinds of questions were used: 'What comes next?' 'What comes before?' 'Does X come before or after Y?' Again a clear-cut distinction emerged between numbers below 4 and numbers above 4. C.G. was completely unable to perform the task for numbers above 4 (0 out of 36 correct answers), while for numbers below 4 she gave 8 out of 8 correct answers for the 'next' questions, 7 out of 8 correct answers for the 'before' questions and 6 out of 8 correct answers for the 'before or after' questions. (The data are given in Table 7.) For pairs composed by a digit below 4 and a digit above 4, she was able to answer 29 out of 40 'before or after' questions.

TABLE 7 NUMERICAL SEQUENCES (PERCENTAGE CORRECT)

	*Numbers 1–4**	*Numbers above 4***
What comes after n?	8	0[§]
What comes before n?	7	0[§]
Does n come before or after y?	6	0[§]

*n = 8. **n = 12. [§]Most answers were 'Don't know'

Summary

These tests show a very clear pattern. If the task involves numbers below 4, apart from zero, then performance was perfect. If it involves numbers above 4, then performance was at floor. This was true for every modality tested. Recognition for arabic numerals and number words, for numbers above 4, appears impossible: the patient is unable to discriminate between the numbers and matched nonsense foils. The production of numbers above 4, also appears impossible: she is unable to recite these number names or count with them. Such clear-item specificity and consistency points to a loss of information from semantic memory, rather than impairments of access that can be overcome by finding a suitable modality or task. Prompts do not appear to help at all in retrieving numbers above 4, which is again evidence for loss of these items.

Tests of the meanings of numbers

The next set of tasks sought to determine whether the meaning of numbers had been preserved, even though it was clear that C.G. was unable to produce or recognize numbers above 4 in any modality.

Knowledge of cardinal values

Cardinality judgements. In this task the patient was asked to compare the numerosity of 2 patterns of different-sized black dots, randomly arranged on pairs of sheets of white paper No explicit knowledge of number names was required for this task, though correct performance needed an understanding of number values.

There were 15 pairs, where each pattern had 4 or fewer dots (e.g. oo versus 0000); 15 pairs of dot patterns from 5 to 10 (e.g oooooo versus 000000); 23 mixed pairs composed of a dot pattern below 4 and a dot pattern from 5 to 10 (e.g. 000 versus oooooo); and finally, there were 10 pairs of dot patterns above 10 (e.g oooooooooooo versus 00000000000). C.G.'s performance (as shown in Table 8), was relatively unimpaired for pairs patterns 4 and below (87% correct answers) and for mixed pairs (96% correct answers). Her performance on pairs of dot patterns from 5 to 10 or above 10 was dramatically impaired (30% correct answers and 40% correct answers, respectively). Response latencies were not recorded on this task, but C.G. appeared to respond very slowly.

An equivalent task using numerals was also carried out, with similar though slightly worse overall performance (*see* Table 8).

TABLE 8 CARDINALITY JUDGEMENTS FOR DOT PATTERN AND NUMERAL PAIRS (PERCENTAGE CORRECT)

	Pairs 1–4	*Pairs 5–10*	*Pairs 10+*	*Pairs 1–4, 5–10*
Dots	87	30	40	96
Numerals	80	13	20	69

Numerosity seriation. In this task the subject was required to order 3 sheets of paper with dot patterns on them, according to the number of dots. Three different kinds of triplets were used: 10 triplets in which each sheet of paper contained a number of dots below 4; 10 triplets in which each sheet of paper contained a number of dots from 5 to 10; and 10 mixed triplets in which each sheet of paper contained numbers of dots from 1 to 10. The 3 different kinds of triplet were randomly presented. Her numerosity seriation ability was relatively good, but not perfect, for triplets of dot patterns from 1 to 4 (80% correct answers), while for triplets composed of dots from 5 to 10 and from 1 to 10 she gave 20% and 60% of correct answers respectively.

Knowledge of number facts

Cardinal facts. Knowledge of exact cardinal number facts was assessed by means of general knowledge questions that everyone might be expected to get right (e.g. 'How many eggs in a dozen?'). For the first 10 questions, answers required the production of numbers above 4. None of C.G.'s answers was correct (e.g. for days in a week? she gave '4'; for freezing-point of water?, she responded 'when it's cold, very cold . . . usually it happens in the refrigerator'). However, in the second set of 10 questions, which tapped facts involving numbers below 4 (e.g. wheels of a car or arms of the cross), the patient was able to get 10 correct answers out of 10 by using an enumeration strategy. Thus for the arms of the cross, she asked the experimenter to hold out her arms and then counted them.

Personal number facts. C.G. was asked 20 questions tapping personal numerical information requiring numbers above 4 (e.g. her shoe size). None of her answers was correct (e.g. to 'how old are you?' she replied, 'I don't know I am a middle aged person').

Non-personal number facts. The patient was asked 20 questions tapping numerical information generally known to all people of a similar background (e.g. the date of Christmas Day). She scored 0 correct out of 20 answers.

Numerical cognitive estimates. Following Shallice and Evans (1978), 10 numerical estimation questions were devised. Here approximate numerical values are required. In none of these spoken questions, were C.G.'s answers correct (e g. to 'What is the hottest temperature of a summer day?', she replied 'Well it's difficult to say . . . 3, 4 centigrade?').

Subitizing

Arrays with up to 4 elements have a special psychological status: the ability to discriminate the numerosity of these arrays is apparently present in infants (Starkey *et al.*, 1990); and adults seem to assign a number to these arrays in a different manner from arrays with more elements (Klahr and Wallace, 1976; *but see* Mandler and Shebo, 1982). The basis for the sparing of numbers up to 4 could be related to the preservation of the apparently primitive ability to perceive numerosities without counting, if indeed C.G. was still able to subitize.

In the test, C.G. was asked to say as quickly as possible, and without explicit counting, how many dots were in a visual array. The dots were always arranged in the canonical way (e.g. :, and ::). Her performance was correct only for the 2-dot pattern, while for the 3-dot pattern she replied 'two' and for the 4-dot pattern she replied 'three'. However, if she was permitted to count she made no errors.

Calculation abilities

The patient had completely lost multiplication tables and was completely unable to carry out even the simplest mathematical operation. Only very simple problems involving not more than 4 fingers or concrete objects (e.g. 'I give you back one of these 4 books, how many books do I have now?') could be resolved using a counting-back or counting-on strategy.

Rapid arithmetical judgement. Following Warrington (1982), a test was devised to assess her ability to check the approximate solutions to arithmetical problems, which could not normally be retrieved from memory. There were 20 problems (5 addition, 5 subtraction, 5 mutiplication and 5 division), all involving 2 to 5 digit numbers. The problems were spoken and the patient instructed to verify, as quickly as she could, the subsequent solution given by the examiner (e.g. $15+19 = 34$). C.G.'s responses were at chance level (8 out of 20), showing that she did not appear to be able to estimate approximate solutions to arithmetical calculations.

Summary

All tests of number meanings show precisely the same watershed as the tests of number processing, namely a total inability to deal with numbers above 4 in any task and in any modality. It should be noted that performance with numbers below 4 was not perfect. It is extraordinary that C.G. should be sometimes unable to compare dot patterns, to name dot patterns or to seriate dot patterns below 4; and indeed to make occasional errors in a task as simple as deciding whether 3 is or is not larger than 1.

Tests of semantic memory

Despite its specificity, the loss of number knowledge may have been part of a more widespread degradation of semantic memory. Several tests were therefore administered to assess whether other categories of knowledge were also affected.

Generation of words from designated semantic categories

The patient was asked to produce as many names as she could remember in 60 s. She was able to give 9 fruit names, 9 animal names and 4 car names. These scores are within the normal range (Novelli *et al.*, 1986).

Picture pointing

Six categories were selected: animals, fruits and vegetables, body parts, musical instruments, vehicles and household objects. The pictures consisted of realistic black and white drawings. The stimuli were presented in 6 arrays of 10 animals, 10 fruits and vegetables, 10 body parts, 10 musical instruments, 10 vehicles and 10 household objects. The patient's task was to point the pictures corresponding to the spoken name. From Table 9A it can be seen the patient's performance was largely unimpaired.

Picture naming

The same material was used in a picture naming task. Her performance was flawless for all the categories presented (*see* Table 9B)

TABLE 9 SEMANTIC MEMORY TASKS (PERCENTAGES OF CORRECT ANSWERS)

A. Picture pointing (n = 60)	
Animals	80
Fruits and vegetables	100
Body parts	100
Musical instruments	90
Vehicles	80
Household objects	100
B. Picture naming (n = 60)	
Animals	100
Fruits and vegetables	100
Body parts	100
Musical instruments	100
Vehicles	100
Household objects	100

Word definitions

C.G. was asked to define a pool of 30 spoken words: 20 concrete words and 10 abstract words. Each class comprised 50% high frequency and 50% low frequency words. C.G. was able to correctly define 16 out of 20 concrete words and 7 out of 10 abstract words.

Semantic anomalies test

Following Baddeley (1976), a test was devised to assess whether C.G. retained semantic information about objects. In Baddeley's test, the sentences all involved the relation between an object and its superordinate category (e.g. 'Are crows fruit?'). However, Warrington (1975) has noted that patients with semantic memory disorders are often able to retrieve superordinate information, but have lost more detailed attribute information. A further set of questions was constructed in which attributes were questioned ('Do foxes have long tails?'). Altogether, 64 sentences were presented auditorily, half required, 'Yes' answers, and half, 'No'; half of the questions referred to the superordinate, while half referred to attributes. The patient's task was to detect the semantic anomalies, C.G.'s performance was again flawless (64 out of 64 correct answers).

Proverbs

We asked the patient to define commonly used proverbs. She was able to give 8 out of 10 correct definitions, which is within the normal range.

Synonyms

The patient was presented with 48 pairs of spoken words. Half of the pairs were unrelated words, and half synonyms. The patient was able to judge which pairs were synonyms for all 48 pairs.

Summary

No general deficit was noted in semantic memory tasks.

Tests of ordinal structure

Deloche and Seron (1984) suggested that a similar structural organization underlies the number series and also other elements with a characteristic order. It is possible that C.G.'s deficit for numbers may be explicable in terms of a deeper problem with ordinal structures generally. In the following tests, the ability of C.G. to reproduce non-numerical sequences was assessed.

Reciting non-numerical sequences

C.G. was asked to recite 5 non-numerical sequences: seasons of the year; musical notes; months of the year; days of the week; letters of the alphabet. The patient was able to recite correctly just the 4 seasons and the 7 musical notes ('Doh, ray, me, etc.'). Performance on the other sequences was poor, e.g. letters: 'c, a, p . . . no more'; days of the week: 'Monday, Wednesday, Friday, Saturday, Sunday'; months of the year, 'December, January, June, May, August').

What comes next?

C.G.'s inability to produce common sequences correctly may have been due to some failure to retrieve accurately and completely information that is still in semantic memory. Two tasks were devised to minimize the retrieval problem for the 3 sequences which she failed to recite correctly. The first task was equivalent to the 'What comes next?' test for the number series described above. In the non-numerical version, the experimenter said the name of an element from the sequence (e.g. 'Monday'), and the patient was asked to give the next one in the sequence. Twenty-five elements were presented (7 days, 12 months and 6 letters). None of C.G.'s answers was correct (e.g. For the letter A, she said, 'I don't know . . . maybe p').

Triplet seriation

In the second task the patient was presented auditorily with 30 triplets taken from the 3 sequences. Ten triplets consisted of letter names, e.g. u, a, g; 10 triplets consisted of days of the week, e.g. Monday, Friday, Wednesday; and 10 triplets of months of the year, e.g. March, January, June. Three words was well within C.G.'s span of immediate word repetition. Her task was to repeat in the correct order the elements of the triplet. C.G. managed just 1 correct answer from 30.

Summary

Familiar sequences, like the alphabet, days of the week and months of the year also pose problems for C.G. She is quite unable to give the next element in these sequences. There are, however, important differences from her performance on equivalent tasks with numbers: where she knows the number names, she is almost always able to provide correct ordinal information, whereas, even though she can recite, say, 5 days of the week in the right order, with gaps, she cannot say what comes next if given 1 day as a prompt.

Tests of knowledge of quantities

Numbers are perhaps most often used to denote quantities, and the meaning of number terms entails their proper ordering with respect to the quantities (cardinal values) denoted by them. It was clear from tests of number meaning, that C.G. showed a total impairment for the cardinal value of numbers above 4. It is possible that this severe deficit could be explicated in terms of a more general cognitive impairment in dealing with quantities. In the following tasks, C.G.'s ability to deal with non-numerical quantities was assessed.

Size judgement task

The first question was whether C.G. could deal with size relations. Sixty pictures of familiar objects were assembled, divided into 5 categories: animals, fruits and vegetables; vehicles; musical instruments; household items, with 12 objects per category. The pictures were realistic black and white drawings all having roughly the same pictorial size; so, for example, a camel and a spider have roughly the same size in the picture. Pairs of pictures from the same category were presented, and C.G. was asked to judge which object was the bigger in real life. The patient responded promptly and without hesitation and her performance was flawless for all categories.

Quantity seriation tasks

Pictures. The same kind of materials were used as in the size judgement task. This time 3 pictures belonging to the same category were presented and the patient was asked to point the pictures of the 3 objects in order of the size of object denoted by the picture. Again her performance was perfect for all categories.

C.G. was also asked to order triplets of playing cards in terms of their usual values. She was able to do this for the picture cards and for the cards 2 to 4; for other values, no triplet was correctly ordered.

Measure terms. The patient was presented with 2 spoken measure terms and was asked to decide which of the 2 terms denoted the greater quantity. Terms denoting weight (e g. gram, kilo, tonellata, quintale) or length (e.g. metre, centimetre, kilometre) were used. Her score was 10 correct out of 10

Judgements of 'more'. The patient was asked to decide which of 2 physical quantities was 'more'. For example, were there more coffee beans or grains of salt in a tea cup? C.G.'s performance was again flawless: she gave 13 correct answers to 13 questions. A second set of questions involved time terms. For example, 'In a year are there more seasons or more months?', or 'In a day, are there more hours or minutes?' By contrast to physical quantities, she was able to reply correctly to just 4 out of 15 questions.

Summary

Generally, C.G. appears to have retained the ability to deal with physical quantities, and can judge which of 2 is larger, either when presented pictorially or verbally A deficit for terms denoting temporal quantities remains.

Tests of formal reasoning

Prerequisites for the development of the concept of number, according to Piaget (1952), include certain specific reasoning abilities. In this next series of tests, C.G.'s ability to carry out the relevant Piagetian reasoning tasks was explored.

Transitivity

In the first task, the patient was asked to make transitive logical inferences. It was a version of a classical Piagetian task in which the patient is shown 2 of the possible pairings of 3 items, A, B and C, of different lengths, for example, A B (with $A > B$), and B C (with $B > C$). She was then asked to determine which member of the third pair (A C) is longer or shorter or bigger or smaller, without being allowed to inspect that pair Her score of correct responses on the critical items was 8 out of 8. In the second task the patient was presented auditorily with pairs of words well-ordered under binary relation, like 'taller than'. The patient was then asked a question about the relation between pairs of words not originally presented in the same clause. For example, the patient would hear, 'John is taller than Fred, and Fred is taller than Peter'; she would then be asked, 'who is the taller, Peter or John?' Her performance was again flawless on 15 questions.

Classification

The ability to classify objects and to ignore irrelevant attributes in classification was a further prerequisite postulated by Piaget. In the first task, the patient was presented with 50 colour photographs of objects representing 10 animals, 10 colours, 10 fruits, 10 household objects and 10 action verbs. The task was to find a way to categorize the photographs. C.G. readily classified the photographs according to their superordinate categories. In the second task, we tested C.G.'s ability to shift criteria in sorting complex stimuli. The stimuli were tokens that varied in colour, shape and size. The patient was first asked to sort the tokens according to an attribute defined by the experimenter (e.g. to sort by colour). The patient was asked to sort by another attribute (e.g. shape), ignoring colour altogether. C G.'s performance on this task was normal, showing that she was able to classify objects according to a given criteria and to shift from one classification to another one, ignoring irrelevant attributes.

Class inclusion

A series of questions based on Piaget's classical class-inclusion task was developed. The patient was asked 10 questions requiring a grasp of the logical relation of class-inclusion (e.g. 'If I have 16 roses and 6 tulips, do I have more roses or more flowers?'). These questions are typically failed by young children. Her performance was correct on all the questions.

One-to-one correspondence

To understand the concept of a cardinal number, Piaget claims that it is necessary for the child to understand that sets will have the same cardinal number if their members can be put in one-to-one correspondence.

Adapting a standard Piagetian test, we gave C G a set of 50 sticks, and asked her to give the same number of sticks to 2, 3, 4, 5 and 6 different persons. C G. was able to carry out the task without any difficulty

Summary

There is no evidence from these tests that C.G suffers an impairment in the kind of logical reasoning competence that has been claimed as necessary for the development of numbers.

DISCUSSION

The patient C.G. presents with the classical signs of Gerstmann's Syndrome: finger agnosia; right-left disorientation; a profound agraphia (but with an equally profound alexia); a remarkably dense acalculia. Apart from these symptoms, she seems fully to have recovered from a stroke 2 yrs prior to testing. In the study reported here, the acalculic condition is examined in detail.

The most noteworthy feature is an apparently total inability to deal with numbers above 4. The inability is present in all the tasks that were administered. She is unable to recognize or produce spoken number words above 4; she is unable to recognize numerals above 4; she cannot understand numbers above 4, nor can she judge which of 2 numbers above 4 is the greater, whether presented as words or as dot patterns; she cannot count above 4, nor recite the number names above 4. Finally, she can retrieve no facts involving numbers above 4. Her ability to deal with numbers below 4 is largely preserved: she can recognize their names and paradoxically, given her total alexia for letters, recognize the numerals; she can count and recite up to 4; she can judge numbers and dot patterns, though with some errors. It is not clear that she can retrieve facts involving numbers below 4: when tested, she appears to construct an image or other representation of the object in question and then enumerates the relevant features (like the arms of the Cross).

Her calculation ability is almost nil, though she can do some additions and subtractions, where the elements and the solutions are 4 or below; but even for the simplest sums she uses a counting-on or counting-back strategy, rather than retrieving the answer from memory.

There is no evidence that her disabilities stem from a wider impairment: semantic memory, apart from numbers, appears intact; her understanding of quantities is also good; and she appears to have preserved the reasoning abilities thought to underlie numbers.

It is true that C.G. shows difficulties with some other ordinal structures. However, these seem to be different from her difficulties with numbers. In particular, she is able to retrieve more than 4 days of the week, and her recitation of letter names, 'C, A, P . . .', does not show a clear dissociation between the first 4 items and the rest. If her only deficit were loss of ordinal structure, one might expect a misordering of preserved numbers, which was not found, and perhaps 'islands' of preservation beyond the first 4 numbers, which also was not found.

It is clear that C.G. suffers a category-specific disability of an unusual type: it is not just that an abstract category, numbers, is selectively affected, but that a definite subcategory is affected.

Impaired access or degraded storage?

Warrington *et al.* and Shallice *et al.* (Shallice, 1988, for a review) have distinguished between impairments of access to stored information from degradation of the store itself such that items of information are actually lost. On the basis of their criteria for item loss it is evident that C.G. has lost the numbers above 4.

Consistency. Within modality of presentation, there is complete consistency by item from test to test: tests involving numbers above 4 are always failed, while tests involving numbers below 4 are almost always correct. Within the verbal modality, she is unable to produce number names above 4, or to understand these names or to recognize them, while she succeeds on verbal tests of numbers below 4. Within the non-verbal (visual) modality, she consistently fails and succeeds with exactly the same numbers: she fails numbers above 4, and succeeds with numbers 4 and below 4.

Depth of processing. It is claimed that degradation of stored information should lead to loss of detailed attribute information, while broad category information may be retained. For numbers that C.G. cannot use, even knowledge that the number terms are numbers also seems lost. However, it is at least arguable that if an item is completely lost, then it will not be possible to recover even superordinate category information.

Priming. No tests of priming as such were carried out. Shallice (1988) maintains that priming should be equivalent to cuing or prompting in activating items that are inaccessible, but not lost. The tests of what comes after N, or what comes before N, show that giving the prior or subsequent number in the series does not help C.G. retrieve that number. Chertkow and Bub (1990) have shown that priming can be effective in a lexical decision task for object names, where cueing is not. It is therefore possible that some residual knowledge about numbers above 4 may be activated using this procedure. We think this unlikely.

Item frequency. The organization of stored information about words and other items is thought to reflect their frequency of occurrence. Frequency effects should be absent, or at least much reduced, if the impairment is in access. The role of item frequency was not explicitly tested in this study, but it is true that the number names and the numerals 1 to 4 are the most frequent in Italian (Bortolini *et al.*, 1972) and English (Kucera and Francis, 1967). However, if the effect simply depended on item frequency, one might expect a more graduated profile of deficit.

On the basis of these criteria, C.G.'s disability entails loss of numbers above 4, rather than impaired access to them.

Modality-specificity and the functional locus of the deficit.

Warrington and Shallice (Shallice, 1987; 1988, for theoretical reviews) have argued that category-specific deficits must be at a locus in the cognitive system where items are assigned to semantic categories, that is, in the semantic system. Since modality effects have been observed, at least for picturable objects, there must, according to this reasoning, be separate semantic systems for the modalities involved. The difficulty in assigning a deficit to the semantic system or systems is well illustrated by Howard and Franklin's (1988) detailed account of single-word processing impairments in the patient M.K. The main problems lie in eliminating systems for item recognition and production that are satellites of a semantic system. In the case of C.G., the issue seems clear in one respect. The deficit to the numbers above 4 appear with complete consistency whatever the task modality. The obvious and natural interpretation is that there is one semantic system, at least for numbers, and that the concepts for numbers above 4 have been lost from it. This interpretation is consistent with the earlier argument that abstract domains will not show modality-specific effects.

If there were 2 semantic systems, a verbal and a non-verbal, then it would have to be argued that exactly the same items had been lost from both. Since Warrington and Shallice have to say that the 2 systems are neurally distinct (hence the observed dissociations), this would seem *a priori* unlikely.

Even more unlikely would be a claim that each of the satellite systems has suffered loss of exactly the same items, that is, the number-word recognition and production systems, the numeral recognition system, and the dot-pattern recognition system, in addition to the item-specific loss of the number concepts.

Two remaining puzzles

If the locus of the deficit lies in the single semantic system for number concepts, then C.G.'s failure to *recognize* number words and numerals above 4 remains unexplained. If the recognition unit for 'sette' (seven) is still intact, why cannot C.G. say, 'This is a word, but I don't know what it means'? And if the recognition unit for '7' is still intact, why can she not recognize it as a familiar symbol, even if she cannot give it a meaning? Auditory lexical decision tests and symbol discrimination tests make it clear that she cannot recognize these items, even as familiar, if now meaningless, ones. It would be implausible, of course, to claim that exactly the same items have been lost from these satellite systems as from the semantic system. One possibility is that a lexical decision judgement [i.e. 'This is a word (not a nonsense syllable)'], or symbol discrimination judgement ['This is a known symbol (not a nonsense shape)'] depends on being able to assign a meaning to the item.

The final puzzle is why the watershed should be between 4 and 5. One possibility has to do with item frequency: the spared numbers are more frequent than those lost. However, to get the sharp division between lost and spared items, requires the additional postulation of a frequency-related threshold, below which items become totally inaccessible. Standard models of word-recognition that posit such a threshold [e.g. Morton's (1969) Logogen model], would also suppose that contextual information, as would be provided by the act of counting, or by prompts, should raise subthreshold items to response levels, at least occasionally. This does not appear to happen. Another possibility is that the meanings of the numbers 1 to 4 are special in some other way, for example, they form the range for perceptual subitizing. However, C.G. is unable to subitize.

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REFERENCES

Baddeley AD (1976) *The Psychology of Memory*. New York: Harper and Row.

Benson DF, Weir WF (1972) Acalculia: acquired anarithmetia. *Cortex*, **8**, 465–472.

Berger H (1926) Über Rechenstörungen bei Herderkrankungen des Grosshirns. *Archiv für Psychiatrie und Nervenkrankheiten*, **78**, 238–263.

Bortolini U, Tagliavini C, Zampolli A (1972) *Lessico di Frequenza della Lingua Italiana Contemporanea*. Milano: Garzanti.

Caramazza A, McCloskey M (1987) Dissociations of calculation processes. In· *Mathematical Disabilities: A Cognitive Neuropsychological Perspective*. Edited by G. Deloche and X. Seron. Hillsdale, NJ: Lawrence Erlbaum, pp. 221–234.

Chertkow H, Bub D (1990) Semantic memory loss in dementia of Alzheimer's type: what do various measures measure? *Brain*, **113**, 397–417.

Cohn R (1961) Dyscalculia. *Archives of Neurology, Chicago*, **4**, 301–307.

Deloche G, Seron X (1982*a*) From one to 1: an analysis of a transcoding process by means of neuropsychological data. *Cognition*, **12**, 119–149.

Deloche G, Seron X (1982*b*) From three to 3. a differential analysis of skills in transcoding quantities between patients with Broca's and Wernicke's aphasia *Brain*, **105**, 719–733.

Deloche G, Seron X (1984) Semantic errors reconsidered in the procedural light of stack concepts. *Brain and Language*, **21**, 59–71.

Deloche G, Seron X (1987) Numerical transcoding: a general production model. In: *Mathematical Disabilities: A Cognitive Neuropsychological Perspective* Edited by G. Deloche and X. Seron. Hillsdale, NJ: Lawrence Erlbaum, pp. 137–170.

Dennis M (1976) Dissociated naming and locating of body parts after left anterior temporal lobe resection: an experimental case study. *Brain and Language*, **3**, 147–163.

De Renzi E, Faglioni P, Ruggerini C (1977) Prove di memoria verbale di impiego clinico per la diagnosi di amnesia. *Archivio di Psicologia, Neurologia e Psichiatria*, **38**, 302–317.

De Renzi E, Faglioni P (1978) Normative data and screening power of a shortened version of the Token Test. *Cortex*, **14**, 41–49.

Dixon RMW (1980) *The Languages of Australia*. Cambridge: Cambridge University Press.

Ferro JM, Silveira Botelho MA (1980) Alexia for arithmetical signs: a cause of disturbed calculation *Cortex*, **16**, 175–180

Gelman R, Gallistel CR (1978) *The Child's Understanding of Number*. Cambridge, MA: Harvard University Press.

Goodglass H, Kaplan E (1972) *The Assessment of Aphasia and Related Disorders* Philadelphia: Lea and Febiger.

Grewel F (1969) The acalculias. In: *Handbook of Clinical Neurology*, Volume 4. Edited by P. J. Vinken and G. W. Bruyn. Amsterdam: North-Holland, pp. 181–194.

Groen GJ, Parkman JM (1972) A chronometric analysis of simple addition. *Psychological Review*, **79**, 329–343.

Hart J, Berndt RS, Caramazza A (1985) Category-specific naming deficit following cerebral infarction. *Nature, London*, **316**, 439–440.

Henschen SE (1919) Über Sprach-, Musik- und Rechenmechanismen und ihre Lokalisationen im Grosshirn. *Zeitschift für die gesamte Neurologie und Psychiatrie*, **52**, 273–298.

Henschen SE (1920) *Klinische und anatomische Beiträge zur Pathologie des Gehirns*. Stockholm: Nordiska Bokhandeln.

Hermelin B, O'Connor N (1990) Factors and primes: a specific numerical ability. *Psychological Medicine*, **20**, 163–169.

Howard D, Franklin S (1988) *Missing the Meaning? A Cognitive Neuropsychological Study of the Processing of Words in an Aphasic Patient* Cambridge, MA: MIT Press.

Jackson M, Warrington EK (1986) Arithmetic skills in patients with unilateral cerebral lesions. *Cortex*, **22**, 611–620.

Klahr D, Wallace JC (1976) *Cognitive Development. An Information-Processing View*. Hillsdale, NJ: Lawrence Erlbaum.

Kleist K (1934) *Gehirnpathologie*. Leipzig: Barth.

KRAPF E (1937) Uber Alkalkulie. *Schweizer Archiv fur Neurologie und Psychiatrie*, **39**, 330–334.

KUČERA H, FRANCIS WN (1967) *Computational Analysis of Present-Day American English*. Providence, RI: Brown University Press.

LURIA AR (1966) *Higher Cortical Functions in Man*. London: Tavistock.

MCCARTHY RA, WARRINGTON EK (1988) Evidence for modality-specific meaning systems in the brain. *Nature, London*, **334**, 428–430.

MCCLOSKEY M, CARAMAZZA A (1987) Cognitive mechanisms in normal and impaired number processing. In: *Mathematical Disabilities: A Cognitive Neuropsychological Perspective*. Edited by G. Deloche and X. Seron. Hillsdale, NJ: Lawrence Erlbaum, pp. 201–219.

MCKENNA P, WARRINGTON EK (1978) Category-specific naming preservation: a single case study. *Journal of Neurology, Neurosurgery, and Psychiatry*, **41**, 571–574.

MANDLER G, SHEBO BJ (1982) Subitizing. an analysis of its component processes. *Journal of Experimental Psychology: General*, **111**, 1–22.

MORTON J (1969) Interaction of information in word recognition. *Psychological Review*, **76**, 165–178.

MORTON J, PATTERSON K (1987) A new attempt at an interpretation, or, an attempt at a new interpretation. In: *Deep Dyslexia*. Second edition. Edited by M Coltheart, K. Patterson and J. C. Marshall. London: Routledge and Kegan Paul, pp. 91–118.

NIELSEN JM (1936) *Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization*. New York: Hoeber.

NOVELLI G, PAPAGNO C, CAPITANI E, LAIACONA M, VALLAR G, CAPPA SF (1986) Tre test clinici di ricerca e di produzione lessicale: taratura su soggetti normali. *Archivio di Psicologia, Neurologia, Psichiatria*, **47**, 477–506.

PIAGET J (1952) *The Child's Conception of Number*. New York: Norton.

RATCLIFF G, NEWCOMBE F (1982) Object recognition: some deductions from the clinical evidence. In: *Normality and Pathology in Cognitive Functions*. Edited by A. W. Ellis. London: Academic Press, pp. 147–171.

RUSSELL B (1903) *The Principles of Mathematics*. Cambridge: Cambridge University Press.

SARTORI G, JOB R (1988) The oyster with four legs: a neuropsychological study on the interaction of visual and semantic information. *Cognitive Neuropsychology*, **5**, 105–132.

SEMENZA C (1988) Impairment in localization of body parts following brain damage. *Cortex*, **24**, 443–449.

SEMENZA C, ZETTIN M (1989) Evidence from aphasia for the role of proper names as pure referring expressions. *Nature, London*, **342**, 678–679.

SHALLICE T (1979) Neuropsychological research and the fractionation of memory systems. In: *Perspectives on Memory Research*. Edited by L. G. Nilsson. Hillsdale, NJ: Lawrence Erlbaum, pp. 257–277.

SHALLICE T (1987) Impairments of semantic processing: multiple dissociations In: *The Cognitive Neuropsychology of Language*. Edited by M. Coltheart, G. Sartori and R. Job. London: Lawrence Erlbaum, pp. 111–127.

SHALLICE T (1988) *From Neuropsychology to Mental Structure*. Cambridge: Cambridge University Press.

SHALLICE T, WARRINGTON EK (1975) Word recognition in a phonemic dyslexic patient. *Quarterly Journal of Experimental Psychology*. **27**, 187–199.

SHALLICE T, EVANS ME (1978) The involvement of the frontal lobes in cognitive estimation. *Cortex*, **14**, 294–303.

SILVERI MC, GAINOTTI G (1988) Interaction between vision and language in category-specific semantic impairment. *Cognitive Neuropsychology*, **5**, 677–709.

STARKEY P, SPELKE ES, GELMAN R (1990) Numerical abstraction by human infants. *Cognition*, **36**, 97–127.

WARRINGTON EK (1975) The selective impairment of semantic memory. *Quarterly Journal of Experimental Psychology*, **27**, 635–657.

WARRINGTON EK (1982) The fractionation of arithmetical skills: a single case study. *Quarterly Journal of Experimental Psychology, A*, **34**, 31–51

WARRINGTON EK, MCCARTHY R (1983) Category specific access dysphasia. *Brain*, **106**, 859–878.

WARRINGTON EK, SHALLICE T (1984) Category specific semantic impairments. *Brain*, **107**, 829–853.

WARRINGTON EK, MCCARTHY RA (1987) Categories of knowledge: further fractionation and an attempted integration. *Brain*, **110**, 1273–1296.

YAMADORI A, ALBERT ML (1973) Word category aphasia *Cortex*, **9**, 112–125.

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TEMPORAL DISSOCIATION OF MOTOR RESPONSES AND SUBJECTIVE AWARENESS

A STUDY IN NORMAL SUBJECTS

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SUMMARY

The aim of the present study was to examine the timing of different responses given simultaneously to a single event, the sudden displacement of a visual object occurring at the onset of the grasping movement directed at that object. The subjects were requested to correct their movement in order to reach accurately for the object and to signal the time at which they became aware of its displacement by a simple vocal utterance (Tah!). The onset of the motor adjustment was measured using kinematic landmarks obtained from the hand trajectory. Movements executed during trials where the object was displaced had an earlier peak in acceleration (107 ms) than movements executed during control trials (120 ms). By contrast, the vocal signal occurred 420 ms following object displacement, that was more than 300 ms after the onset of the motor correction. Control experiments were performed in order to verify the influence of possible interferences between the two tasks. Motor corrections performed without vocal utterance had the same timing as when the vocal signal was produced. Vocal signals produced in response to object's displacements but in the absence of reaching movements had the same latency as when movements were performed. We conclude from these results that the two responses were generated independently of each other. Assuming that the vocal responses in this experiment did signal the subject's awareness, the observed delay between motor corrections and these responses suggests that neural activity must be processed during a significant and quantifiable amount of time before it can give rise to conscious experience. This dissociation between motor responses and awareness in normal subjects is discussed in the light of clinical cases where overt behaviour and conscious experience are dissociated by cerebral lesions.

INTRODUCTION

The fact that motor responses to a sensory stimulus can be generated in the absence of an overt perceptual experience of the stimulus, is well established. In the visual modality, pathological conditions offer a typical example of such a dissociation between motor and perceptual responses. Patients with scotomata resulting from lesion of the primary visual cortex have been shown to be able to point (by hand or by eye) with relatively good accuracy to unseen visual targets appearing within the blind area of their visual field (e.g. Weiskrantz *et al.*, 1974; Perenin and Jeannerod, 1978).

Similar phenomena can also be observed in normal subjects, for example, in experimental situations where the visual target to which a subject is responding is briskly displaced. It has been shown that, if the target shift is triggered during a voluntary saccade, the subjects remain unaware of the displacement, yet they can point correctly at the final target location (Bridgeman *et al.*, 1979). Goodale *et al.* (1986) also reported a

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pointing experiment where the target occasionally made jumps of several degrees, triggered by the saccade that immediately preceded the movement of the hand, and thus unnoticed by the subjects. They found that subjects were nonetheless able to adjust the trajectory of their moving hand in order to reach the target. Interestingly no additional time was needed for producing the correction, and no secondary movement was observed, suggesting that the visual signals related to the target shift were used without delay for adjusting the trajectory. These experiments confirmed and extended previous observations where accurate visuomotor responses directed at visual targets were clearly dissociated from inaccurate subjective reports about the localization of these targets (e.g. Skavenski and Hansen, 1978; Stark and Bridgeman, 1983). Finally, recent experiments also support the idea that different aspects of the same stimulus are clearly dissociable at the perceptual level. In Taylor and McCloskey's (1990) experiment, subjects were presented with a small visual target to which they had to respond by an arm movement. In some of the trials, the target was masked by a larger stimulus presented 50 ms later. Despite the fact that the target was not consciously perceived, the motor response was nevertheless produced with the same latency as in the control situation. Similar findings were made by Meeres and Graves (1990), who showed that subjects were able to report the correct location of targets that remained 'unseen', a dissociation which recalls that observed in blindsight patients.

The above experiments thus provide an experimental demonstration of the commonly accepted fact that motor responses can be given to non-consciously detected stimuli. The potential interest of such observations, however, is that they might represent extreme cases of a more general phenomenon. Indeed, it is quite possible that some degree of dissociation between overt motor responses to stimuli and the subjective experience of these stimuli would exist as a common feature of our daily experience. In other words, such a dissociation, if it could be demonstrated and quantified, would reveal the existence of two normally separate (and possibly parallel) modalities of processing external events, leading respectively to two widely different types of output. Designing an experimental situation where both the motor and the subjective responses would be present could thus produce an interesting paradigm for studying neural mechanisms involved in poorly known aspects of mental functioning, like awareness.

One condition where a dissociation between these two modalities of processing could possibly appear is the condition where subjects would be required to produce simultaneously two responses to the same stimulus, one related to their performance in a motor task, and the other based on their perceptual awareness. Such a situation would allow measurement of the temporal relationships between the two responses, and some inference to be made about the nature of the mechanisms respectively involved. Paulignan *et al.* (1990) have reported an observation which strongly suggests this possibility. Subjects were instructed to track by hand the displacements of a visual object. Objects' displacements, when they occurred, were time-locked to the onset of subjects' movements, so that subjects had to make fast corrections in order to reach the object. Indeed, they were found to be able to amend the trajectory of their hand within about 100 ms. However, when asked at the end of the session to estimate at which point of their movement they had seen the displacement, the subjects consistently reported the impression that the object jumped near the moment when they were to touch it, that is, much later than the actual occurrence of the object displacement and than the onset of their own corrective movement.

The same situation was used in the present experiments for obtaining an objective measurement of the relative timing of the motor and the perceptual responses. The motor response was measured through a kinematic analysis of the visuomotor adjustment, and the perceptual experience was inferred from a vocal signal produced by the subject in relation to the perceived change in object position.

GENERAL METHODS

Subjects

Six subjects (3 males and 3 females) participated in the experiments. They were all right-handed, had normal or corrected vision and were naive as to the purpose of the experiment.

Experimental conditions

Several conditions were used. The complete experiment, where both the motor response and the perceptual responses were requested from the subjects will be referred to as the 'main experiment'. Control experiments, however, were systematically performed on the same subjects, in order to quantify the degree of interference between the two responses. These controls involved conditions where the subjects had to produce either the motor response or the perceptual response alone. The order of presentation of the main and the control experiments was counterbalanced across subjects in order to avoid sequential effects.

Apparatus

Subjects were seated comfortably, without restraint, facing the working surface in a dimly lit room They placed their right hand at the starting position in front of the body midline. The hand rested on its ulnar edge, with the tip of the index and the tip of the thumb maintained in contact with each other. A start switch was placed next to the thumb, so that it was activated immediately when the hand left the starting position. The target-objects were three dowels (10 cm high, 1.5 cm in diameter), made of translucent material, placed at 10°, 20° and 30° respectively, to the right of the subject's midline. Distance of the targets with respect to the hand was 35 cm. The dowels were placed upright on the working surface and were illuminated from below by computer controlled light emitting diodes embedded within the table surface.

The subjects were instructed to reach, grasp and lift the dowel rapidly and accurately, using the distal pads of the thumb and index finger in a precision grip (Napier, 1956). Prior to the first session, they received a few practice trials for testing their comprehension of the instructions.

Recording of hand movements

Prehension movements were recorded bidimensionally by a Selspot-System camera equipped with a 50 mm lens, placed 3 m above the horizontal working plane. The camera monitored the displacements of 4 infrared emitting diodes (IREDs) placed on the right arm in the following positions: (1) on the medial lower corner of the thumb nail; (2) on the lateral lower corner of the index finger nail; (3) on the skin immediately proximal to the styloid process of the radius at the wrist; and (4) on the skin above the cubital head at the elbow.

Dynamic accuracy tests indicated that the spatial precision of the measures was within 2 mm. A second-order Butterworth dual-pass filter with a highpass cut-off frequency of 8 Hz was used for data processing. X and Y trajectories of the IREDs were computed after filtering. Tangential velocity of the wrist IRED was then computed. Acceleration data were derived by differentiating the velocity data. Movement time (MT) was measured at the time interval between the onset of the thumb IRED movement, and the time when the fingers came in contact with the dowel (Fig. 1). Spatiotemporal variability of the wrist trajectory was quantified after normalization of the data in time The standard deviations of the mean X and Y positions of the wrist IRED were calculated for each of the 100 normalized frames. This provided a representation of variability of the spatial path in normalized time. In addition, to obtain a global estimate of variability (index of variability) for the wrist IRED in each condition, the surface area of the ellipses defined by the standard deviations in X and Y dimensions was computed (in cm^2), and the values of these surfaces in each frame were pooled (Georgopoulos *et al.*, 1981).

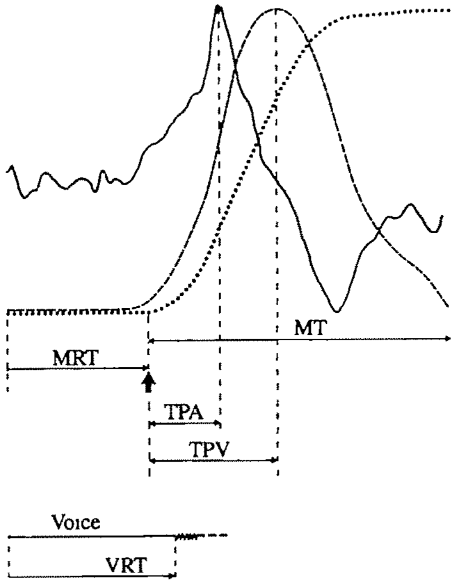

FIG. 1. Parameters drawn from kinematic analysis for comparing blocked, control and perturbed trials Wrist position, velocity and acceleration are represented diagrammatically during one control trial. Beginning of the curves corresponds to illumination of the dowel MRT = motor reaction time, MT = movement time, TPV = time to peak velocity; TPA = time to peak acceleration. Vertical arrow at onset of movement indicates the time at which dowel displacement occurs in perturbed trials *Lower row* voice recording. VRT = vocal reaction time

Recording of the vocal responses

The vocal response was intended to be devoid of verbal content (Tah!). It was recorded by a microphone positioned near the subject's mouth. The vocal signal was fed into a Schmidt trigger and transformed into an analogical pulse sampled at 200 Hz.

MAIN EXPERIMENT

Procedure

This experiment was run in two sessions.

In the first session, three counterbalanced blocks of trials were run by illuminating the dowel at a single location (e.g. at 10°, 20° or 30°) 10 consecutive times (*blocked* trials). The illumination of a dowel was the signal for the subject to start the hand movement. Motor reaction times (MRTs) were measured as the delay between illumination of the dowel and onset of the thumb displacement. This landmark was chosen because, in this experiment, the thumb appeared to be displaced slightly before the wrist. In addition, the subjects were instructed to emit a vocal response as soon as they saw one of the dowels illuminated. Vocal reaction times (VRTs) were measured as the delay between illumination of the dowel and onset of the vocal response (Fig. 1).

In the second session, a single block of 100 trials was run. Each single trial during this run started with illumination of the dowel placed at the centre of the array (20°). For 20% of the trials, the light was unexpectedly shifted from the central dowel to the one placed to the right (30°) or to the left (10°). These were *perturbed* trials (PR for trials perturbed to the right, PL to the left). The shift was produced by the release of the start switch when the hand left its resting position, that is, it occurred within a few milliseconds following movement onset. Since the room was dimly lit, the appearance was that of an instantaneous shift in the position of the central dowel by 10° either to the left or to the right. For 80% of the trials no perturbation occurred (the central dowel remained illuminated throughout). These were *control* trials.

Subjects were instructed to track the position of the dowel and to grasp it. MRTs in response to illumination of the first dowel were measured as in the first session. The onset of the motor adjustment in response to the target shift was measured by using kinematic landmarks picked up from the trajectory of the hand (*see below*). Subjects were also instructed to emit a first vocal response when they saw the central dowel illuminated, and a second one if and when they saw it being shifted to the right or to the left. VRTs in response to illumination of the first dowel (VRT1) were measured as in the first session. VRTs in response to the dowel shifts (VRT2) were measured as the delay between the release of the start switch (which triggered the shift in dowel position at the onset of the hand movement) and onset of the second vocal response.

In both sessions, the two tasks (motor and vocal) were therefore performed simultaneously. The subjects were informed that both were of equal importance.

Results

Only the results concerning the transport component will be described here. The results concerning the grasp component, which are irrelevant to the present study, will not be reported in detail. A complete description of finger trajectories has been given in another paper (Paulignan *et al.*, 1991*a*). The present results conformed in every respect to this description.

The results will be presented as inter-subject means. This procedure, which integrates inter-subject variability, explains the relatively high standard deviations. In individual subjects, standard deviations were lower: in spite of the relatively small number of trials in some of the blocks, coefficients of variations ranged between 1% and 6% for the main parameters.

Blocked trials

Motor reaction time. Mean MRT was about 300 ms. There was no significant difference between MRTs for different dowel locations ($P > 0.25$, paired t test) (Table 1).

Movement time. MT was not significantly affected by target position ($P > 0.25$, paired t test). The values of this parameter ranged between 560 ms and 600 ms for movements directed at 10°, 20° or 30° (Table 1).

Kinematics of wrist movement. The kinematics of the IRED located at the wrist were used as an index for describing the transport component of the prehension movement. The wrist movements had asymmetric velocity profiles. As shown in Fig. 2 (*upper part*), the time to peak velocity of the wrist (parameter TPV) was reached within 30–40% of total movement time. The mean TPV was 224 ms (Table 1). The values of time to peak acceleration (parameter TPA) were around 120 ms and were also quite similar for the three dowel positions (Table 1).

Spatial path and variability of wrist trajectory. The wrist path in the X, Y phase plane, as studied through the displacement of the wrist IRED, tended to be rectilinear (Fig. 2, *lower part*).

The spatiotemporal variability of the wrist trajectories across trials was relatively low (*see below*). Indices of variability for the spatial paths were 126 cm^2 for movements directed at the 20° dowel (121 cm^2 for 10° and 139 cm^2 for 30°).

TABLE 1 INTER-SUBJECT MEAN· MOTOR REACTION TIMES, VOCAL REACTION TIMES AND KINEMATIC CHARACTERISTICS OF TRANSPORT COMPONENT (MT, TPA AND TPV) DURING BLOCKED TRIALS

	MRT	*MT*	*TPA*	*TPV*	*VRT*
B10	303	600	118	228	371
	(76)	(96)	(27)	(46)	(76)
B20	297	560	123	225	382
	(54)	(81)	(32)	(32)	(60)
B30	306	588	118	220	375
	(65)	(89)	(31)	(33)	(55)

B10 = blocked trials, movements directed at the left dowel (10°); B20 = blocked trials, movements directed at the middle dowel (20°); B30 = blocked trials, movements directed at the right dowel (30°); MRT = motor reaction time; MT = movement time, TPA = time to first peak of acceleration, TPV = time to first peak of velocity; VRT = vocal reaction time, SDs in parentheses.

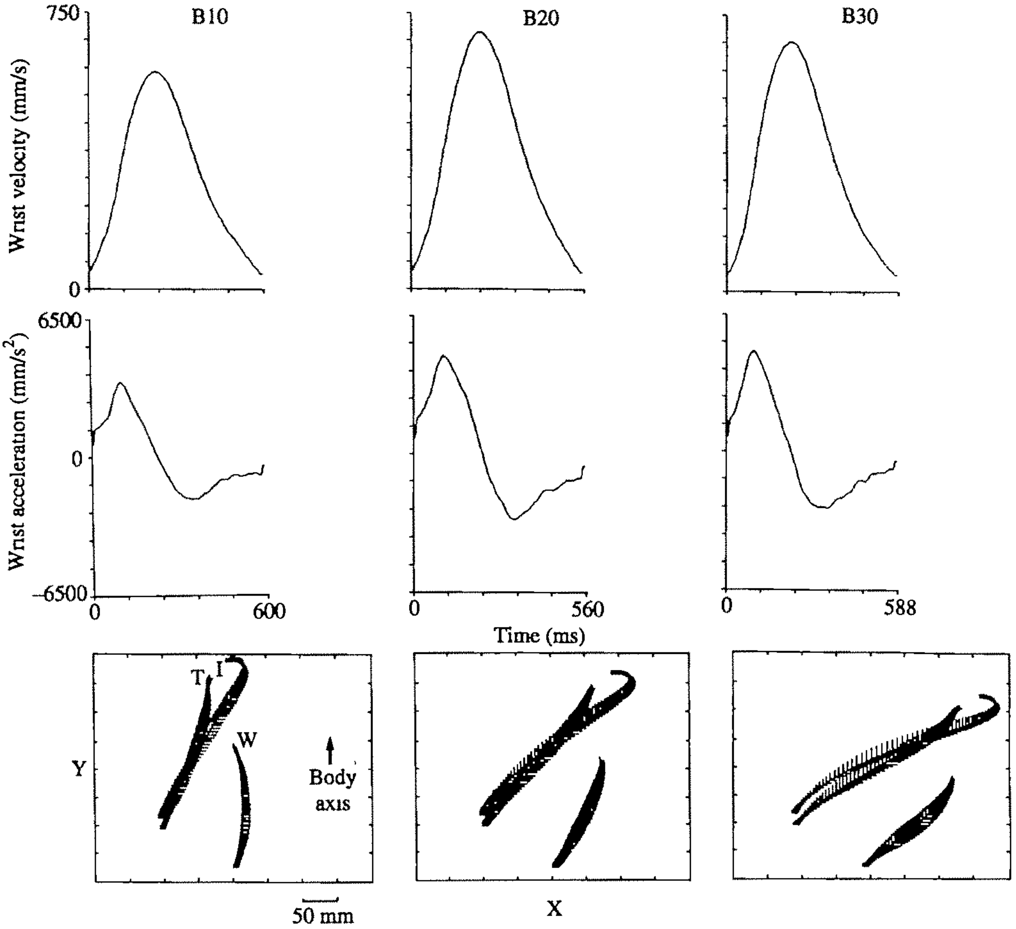

FIG. 2 Kinematic pattern and spatial path of prehension movement in blocked trials *Upper two rows* velocity and acceleration curves of the wrist IRED averaged from all subjects during movements directed at the 10°, 20° or 30° dowels (B10, B20, B30, respectively) Note normalized time-scale due to averaging Mean value of movement duration (in ms) is indicated below each graph. *Lower row*· XY spatial path averaged from all subjects in the same 3 conditions. In these graphs, movements are seen from above W = trajectory of the wrist IRED, I = index finger, T = thumb. Note formation of finger grip by closure of fingers prior to contact with objects. Closure is mostly effected by index finger. Small bars on the trajectories indicate X and Y standard deviations with respect to mean trajectory, for each of the 100 frames of analysis. Note greater variability near the middle of the path and low variability at the time of contact with object

Vocal responses. The reaction time for the vocal responses (VRT) was used as an index of perception of the target by the subjects. There were no significant differences among VRTs for the three target locations ($P > 0.25$, paired *t* test). The values of VRTs (around 375 ms) were found to be systematically longer (by about 70 ms) than those of the corresponding MRTs (Table 1).

Control trials

Control trials were obtained during the second experimental session, as the unperturbed trials directed at the 20° dowel (C20) intermixed with the perturbed trials. A comparison of these control trials with the blocked trials directed at the same 20° dowel during the first session can be made by comparing the B20 values in Table 1 with the C20 values in Table 2.

This comparison reveals that the temporal values of the kinematic parameters used for describing the transport component (MT, TPA and TPV), of the motor reaction times (MRTs) and the vocal reaction times (VRTs) were within the same range for the blocked and the control trials ($P > 0.5$ for MT; $P > 0.25$ for TPA; $P > 0.25$ for TPV; $P > 0.25$ for MRTs and $P > 0.25$ for VRTs, paired t test).

In addition, the kinematic study showed that trajectories of the wrist during the control trials did not differ from those recorded in the blocked trials for the corresponding dowel location (Fig. 3, C20) The spatiotemporal variability of the wrist for the C20 trials (196 cm^2) was not significantly different from that for the movements directed at the corresponding location in the blocked trials (B20) ($P > 0.5$, paired t test).

Perturbed trials

Perturbed trials represented 20% of the total number of trials during the second experimental session (i e. 20 trials per subject). In 10 trials the target jumped from the 20° to the 10° target (PL). In 10 trials, it jumped from the 20° to the 30° target (PR) These perturbations had little effect on final accuracy, very few trials were observed where the subjects failed to grasp the dowel correctly.

Motor reaction time. MRTs were not significantly increased during perturbed trials with respect to the control trials ($P > 0.5$, paired t test) (Table 2).

Movement time. The duration of movements during perturbed trials was consistently and significantly increased with respect to movements during control trials. This increase amounted to 125 ms in PL trials and 124 ms in PR trials (Table 2).

Spatial path and kinematics of wrist movement. A sharp change in direction of the wrist movement was observed in response to the perturbation, in order for the hand to reach the new dowel location (Fig. 3, *lower row*). This change in direction occurred on average 329 ms (SD = 45 ms) and 357 ms (SD = 46 ms) following the beginning of movement, for PL and PR trials, respectively. As a consequence of the change in direction, these movements appeared to be composed of two submovements, the first one directed at the location of the initial target (20°), and the second one at the location of the new target.

The kinematic study revealed that parameters TPA and TPV of the first submovements occurred earlier than TPA and TPV of movements in control trials. Although these differences between perturbed and non-perturbed movements were relatively small (e.g around 16 ms for TPA) they were consistent and statistically significant (Table 2). Figure 4A, where acceleration curves in control and perturbed trials are compared, gives an illustration of this result. This figure also shows that the whole kinematic structure of the movement was reorganized as a consequence of the perturbation· the deceleration following the acceleration peak was faster than in control movements, the peak deceleration occurred earlier, and a secondary acceleration was present.

Spatiotemporal variability of the wrist movements during the perturbed trials was increased with respect to control trials. The mean indices of variability were 238 cm^2 for PL and 255 cm^2 for PR trials. These values were significantly different from the control values ($P < 0.05$).

Vocal responses. In perturbed trials where the 20° dowel was first illuminated and where the light then jumped to the 30° dowel (PR trials) or to the 10° dowel (PL trials), subjects emitted two vocal responses. The first one was related to illumination of the first dowel, and the second one to the illumination of the second dowel. Vocal reaction times to illumination of the first dowel (VRT1) in perturbed trials were not significantly different from VRT in control trials ($P > 0.25$, paired t test, Table 2). Vocal reaction times in response to illumination of the second dowel (VRT2) were 420 ms on average. On some occasions, the dissociation between motor and vocal responses was such that subjects, to their own surprise, were already lifting the dowel while they emitted the vocal response. The values of VRT2 in PL and PR trials were not significantly different from each other ($P > 0.25$, paired t test, Table 2). VRT2 was longer than VRT1, but this difference was not significant ($P > 0.25$, paired t test)

The relation of the second vocal to the second dowel was unambiguously confirmed by the fact that, in non-perturbed trials (where only the first dowel was illuminated), no cases in which the subjects emitted a second vocal response were observed.

Covariation of motor and vocal responses. The degree of temporal correlation between the occurrence of motor and vocal responses obtained during the second session was examined on a single trial basis using a linear regression test. A relatively high degree of correlation was found between MRT and VRT1. For C20 trials, the correlation was $r = 0.57$, for PR trials, $r = 0.66$, and for PL trials, $r = 0.75$. By contrast,

TABLE 2 INTER-SUBJECT MEAN MOTOR REACTION TIMES, VOCAL REACTION TIMES AND KINEMATIC CHARACTERISTICS OF TRANSPORT COMPONENT (MT, TPA AND TPV) DURING MAIN EXPERIMENT

	MRT	*MT*	*TPA*	*TPV*	*VRT1*	*VRT2*
C20	327	611	120	238	381	–
	(80)	(86)	(29)	(43)	(56)	–
PR	330	735***	103***	212**	388	417
	(82)	(82)	(21)	(34)	(63)	(43)
PL	325	736***	110**	213**	385	422
	(69)	(77)	(25)	(37)	(81)	(57)

C20 = control trials, PR, PL = trials perturbed to the right and to the left, respectively; MRT = motor reaction time; MT = movement time; TPA = time to first peak of acceleration; TPV = time to first peak of velocity; VRT1 = vocal reaction time in response to the first target (20°), VRT2 = vocal reaction time in response to the second target (PR = 30°, PL = 10°); values significantly different from control values $^{**}P < 0.005$, $^{***}P < 0.0005$; SDs in parentheses.

no correlation was observed between kinematic landmarks of the wrist trajectory and VRT2. Coefficients of correlation between TPA and VRT2 were $r = 0.29$ for PR trials and $r = 0.04$ for PL trials Between TPV and VRT2 they were $r = 0.14$ for PR trials, and $r = 0.04$ for PL trials.

CONTROL EXPERIMENTS

The results of the main experiment were obtained using a dual-task procedure. Traditionally dual-task procedures are used to make inferences about the attention demands of one of the two tasks (Posner and Boies, 1971; Keele, 1973; Kerr, 1973). In our experiment we emphasized in the instructions to the subject that both tasks were of equal importance.

However, in order to assess more clearly the respective independence of the motor and the vocal responses, it appeared necessary to measure the temporal characteristics of each response separately, i.e. the motor response in the absence of the vocal response, and the vocal response in the absence of the motor response. This was undertaken in five control experiments using the same subjects as in the main experiment. As previously mentioned the sequence of the main experiment and of each of the control experiments was counterbalanced between subjects in order to prevent sequential effects.

Control experiment 1

The aim of this experiment was to compare the kinematic parameters of the motor response in blocked, control and perturbed trials performed without the vocal response, to those recorded during the main experiment The procedure was identical to that of the main experiment except for the fact that the subjects were not instructed to emit vocal responses on illumination or displacement of the dowels.

Results concerning the blocked, control and perturbed trials from this control experiment were interesting in that they closely replicated those of the main experiment. These results are shown in Table 3.

MRTs during the perturbed trials did not differ from those during the control trials ($P > 0.25$, paired t test). As expected, the durations of movements in perturbed trials were consistently and significantly increased with respect to movements in control trials. This increase amounted to 149 ms in PL trials and 153 ms in PR trials (Table 3). These differences were within the same range as the differences observed in the main experiment ($P > 0.5$, paired t test).

The values of the kinematic parameters of the transport component are also shown in Table 3. As in the main experiment, parameter TPA was shorter in perturbed trials than in control trials (Fig. 4B). In perturbed trials, the change in direction of the wrist spatial path occurred 332 ms (SD = 51 ms) and 341 ms (SD = 63 ms) after perturbation to the left and to the right, respectively. Spatiotemporal variability of

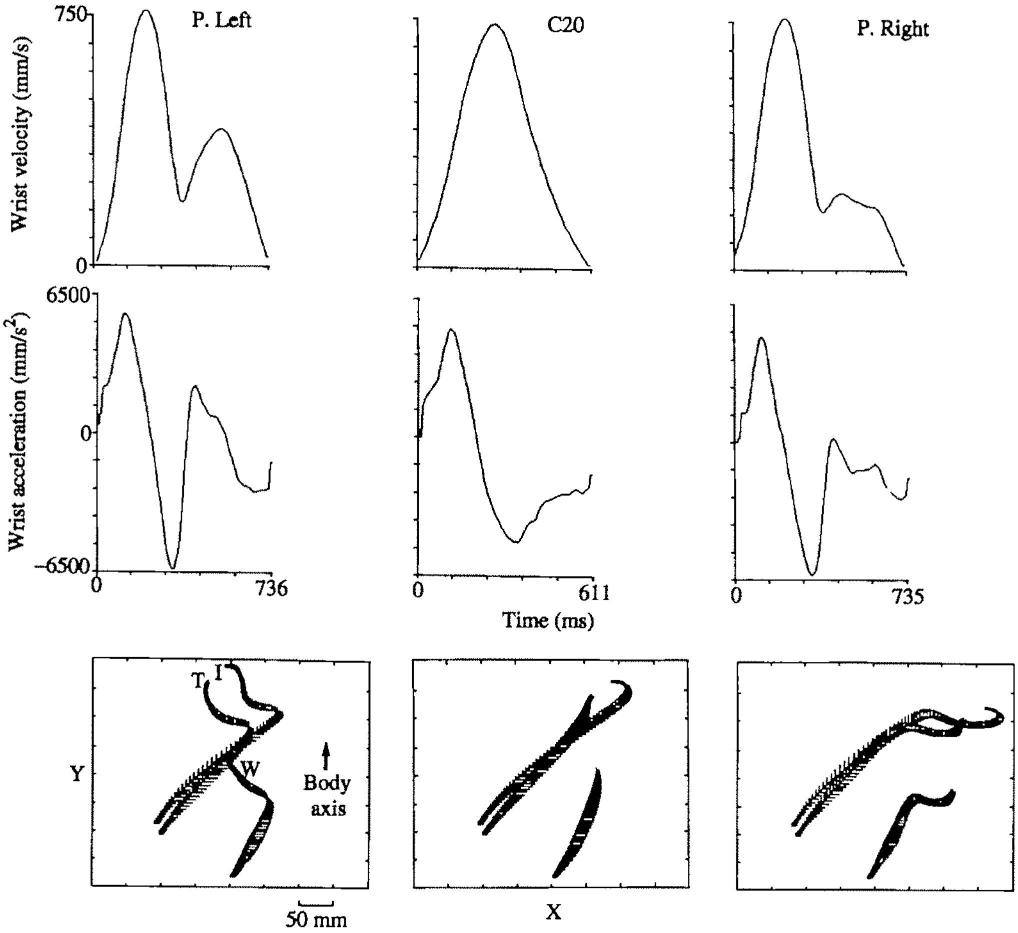

FIG. 3 Kinematic pattern and spatial path of prehension movements in control and perturbed trials. *Upper two rows*: velocity and acceleration curves of the wrist IRED averaged from all subjects. C20· control trials directed at the 20° dowel P. Left = perturbed trials where the light was displaced from the 20° to the 10° dowel (to the left). P. Right = the light was displaced from the 20° to the 30° dowel (to the right). Note normalized time and indication of mean movement time below each graph. Also note sharp deceleration of wrist following perturbations and reinitiation of a corrective movement in the new target direction *Lower row*: XY spatial path averaged from all subjects. Same legend as in Fig 2.

the wrist movements during the perturbed trials was significantly increased with respect to control trials. The mean indices of variability were 259 cm^2 for PL and 224 cm^2 for PR trials. These values were larger than the control value (196 cm^2, $P < 0.05$, paired t test).

These results therefore demonstrate that the motor task of grasping the dowels in the unperturbed and in the perturbed trials was not affected by whether a concomitant perceptual task was required from the subjects or not.

Control experiment 2

The aim of control experiment 2 was to have a baseline measure for vocal reaction time. Subjects were asked to emit a vocal signal in response to the illumination of the dowel positioned at 20° without moving the hand. The mean VRT was 382 ms (Table 4). This result is complementary to that of control experiment

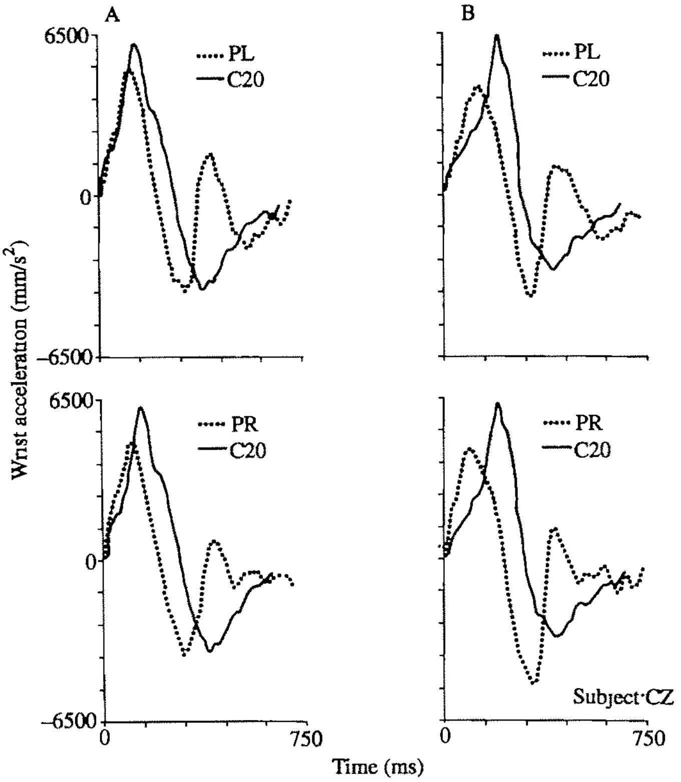

FIG. 4 Wrist acceleration curves in control and perturbed trials. Single trial acceleration curves from subject CZ have been superimposed. Continuous line = control trials (C20); dotted line = perturbed trials. *Upper row*, perturbed to the left (PL); *lower row*, perturbed to the right (PR) A, samples from main experiment; B, from control experiment 1.

1, in showing that the timing of the vocal response used as an index of the perceptual task was not affected by whether a concomitant motor task was performed or not.

Control experiment 3

Control experiment 3 was carried out for evaluating the motor reaction time alone, i.e. in the absence of execution of the full movement and in the absence of a vocal response. Subjects did not have to make a reaching movement toward the dowels nor to emit vocal responses at their illumination. They were instructed only to release the switch on illumination of the 20° dowel. Mean MRT was 331 ms (SD = 51 ms) (Table 4).

Control experiment 4

It also appeared important to test whether the second vocal response used as an index for perception of the target shift was influenced or not by the presence of the first vocal response. The procedure was the same as in the main experiment except that the subjects were instructed not to emit vocal responses to the illumination of the first dowel (20°). The reaching movements were performed by the subjects as in the main experiment or in control experiment 1, but were not recorded. The mean MRT was 330 ms (SD = 69 ms). The values of VRT2s in PL and in PR trials were similar (421 ms and 419 ms, respectively, $P > 0.5$, paired t test) (Table 4). This result demonstrates that the timing of the second vocal response, related to the shift of the dowel at the onset of the movement, was not affected by whether or not it was preceded by the first vocal response.

TABLE 3 INTER-SUBJECT MEAN MOTOR REACTION TIMES, MOVEMENT TIMES, TIME TO PEAK ACCELERATION AND TIME TO PEAK VELOCITY DURING CONTROL EXPERIMENT 1

	MRT	*MT*	*TPA*	*TPV*
B10	298 (57)	629 (40)	119 (28)	222 (22)
B20	301 (44)	563 (45)	127 (25)	244 (27)
B30	293 (48)	605 (30)	118 (29)	256 (22)
C20	324 (80)	583 (75)	114 (21)	224 (43)
PR	328 (73)	736*** (97)	99* (29)	193* (37)
PL	321 (56)	732*** (67)	104* (15)	195* (28)

B10 = blocked trials, movements directed at the left dowel (10°), B20 = blocked trials, movements directed at the middle dowel (20°); B30 = blocked trials, movements directed at the right dowel (30°); C20 = control trials, PR, PL = trials perturbed to the right and to the left, respectively; MRT = motor reaction time, MT = movement time, TPA = time to first peak of acceleration, TPV = time to first peak of velocity; values significantly different from control values *$P < 0.05$, ***$P < 0.0005$, SDs in parentheses.

TABLE 4 INTER-SUBJECT MEAN MOTOR REACTION TIME AND VOCAL REACTION TIME IN CONTROL AND PERTURBED TRIALS FOR MAIN AND CONTROL EXPERIMENTS

	Main experiment			*Control experiment 1*	*Control experiment 2*	*Control experiment 3*	*Control experiment 4*		*Control experiment 5*		
	MRT	*VRT1*	*VRT2*	*MRT*	*VRT1*	*MRT*	*MRT*	*VRT2*	*MRT*	*VRT1*	*VRT2*
C20	327 (80)	381 (56)	– –	324 (80)	382 (33)	331 (51)	328 (61)	– –	323 (32)	383 (57)	– –
PR	325 (69)	388 (63)	422 (57)	321 (56)	– –	– –	334 (73)	419 (73)	327 (53)	390 (64)	414 (57)
PL	330 (82)	385 (81)	417 (43)	328 (73)	– –	– –	328 (79)	421 (72)	321 (47)	400 (61)	427 (57)

C20 = control trials; PR, PL = trials perturbed to the right and to the left, respectively; MRT = motor reaction time, VRT1 = vocal reaction time to the first target (20°); VRT2 = vocal reaction time to the second target (PR = 30°, PL = 10°), SDs in parentheses.

Control experiment 5

Control experiment 5 was complementary to control experiment 1. Its aim was to compare VRTs in control and perturbed trials in the absence of execution of the full reaching movements, and to further exclude a possible influence of execution of the motor task on the emission of vocal responses. The procedure was similar to that of control experiment 3. Subjects were instructed to release the switch without executing the reaching movement toward the dowels, and only to emit vocal responses on illumination and displacement of the dowels.

The mean MRT was 323 ms (SD = 49 ms). VRT1s in control trials were within the same range as in perturbed trials ($P > 0.5$, paired t test) VRT2s in PR and PL trials were also within the same range ($P > 0.25$, paired t test) (Table 4). These results confirm the minimal interference between motor and vocal responses.

COMPARISON OF MAIN AND CONTROL EXPERIMENTS

An analysis of variance was made to compare the values of the parameters MRT, TPA and VRT from the main experiment with the values of the same parameters found in control experiments.

Motor reaction time. MRTs were entered into a one-way repeated measures ANOVA in which the factor was experiment (main, control 1, control 4 and control 5). MRTs were not significantly different across the four experimental sessions, F(1,5) = 3.045, $P > 0.25$. This result indicates a high stability of MRTs whether the full movement was performed or not, and vocal responses were emitted or not.

Time to peak acceleration. An ANOVA was carried out to compare parameter TPA in main experiment and in control experiment 1 for control (C20) and perturbed (PL and PR) trials. No interactions were significant: experiment×TPA×C20, F(1,5) = 1.782, $P > 0.25$, experiment×TPA×PL, F(1,5) = 0.518, $P > 0.25$; experiment×TPA×PR, F(1,5) = 0.003, $P > 0.25$. This result demonstrates that the kinematics of the reaching movements were not affected by whether the vocal response was emitted or not

Vocal reaction times. VRT1s were entered into a one-way repeated-measures ANOVA in which the factor was experiment (main, control 2 and control 5): F(1,5) = 0.189, $P > 0.25$.

The same test was used for VRT2 with experiment as the factor (main, control 4 and control 5); F(1,5) = 0.12, $P > 0.25$.

Finally, the values of VRT1s and VRT2s were compared using also a one-way repeated-measures ANOVA in which the factor was experiment (main and control 1): F(1,5) = 2.012, $P > 0.25$. None of these analyses gave significant interactions.

DISCUSSION

In the present experiments, subjects started to move their hand some 325 ms after stimulus onset. This delay corresponds, at least in part, to the time needed for establishing a motor program for accurately reaching the selected dowel. When a shift of the dowel position occurred synchronized with movement onset, this program had to be corrected in order for the movement to change its direction and to reach the new dowel position. Our results show that the time required for correcting the program was much shorter than the time needed for establishing it. Kinematic analysis of the movement revealed that the acceleration resulting from the initial program was stopped shortly after movement onset, so that peak acceleration appeared to occur earlier than in the unperturbed movements. The difference in time to peak acceleration between the two conditions was relatively small (about 15 ms), but it was clearly significant. In addition, this finding, which was repeated twice in the present study (in the main experiment and in control experiment 1), fully confirmed the original description of the same phenomenon made by Paulignan *et al.* (1990, 1991*a*). Thus, the minimum amount of time needed for the subjects to begin to react to the shift in dowel position (termed here as the motor response) can be evaluated at about 100–110 ms. This value is within the range of minimum durations reported by other authors for a stimulus to influence an ongoing movement [for a visual stimulus, *see* Zelaznik *et al.* (1983); for a proprioceptive stimulus, *see* Crago *et al.* (1976)].

Simultaneously with performing their reaching movement subjects were instructed to signal vocally the illumination of the dowels. This vocal utterance had no verbal content and was unrelated to the nature of the stimulus. Its only function was for the subjects to signal their conscious experience of the visual change. Therefore we assumed that this response was indeed related to subjects' awareness of the change in dowel position, and was not just another motor response triggered by the stimuli. This assumption is supported by at least two arguments. First, the long duration of VRT2 corresponded to the impression reported by the subjects in this and in the Paulignan *et al.* (1990) experiment: subjects consistently 'saw' the dowel changing its position when they were completing their correction movement, and not when they were initiating it. In addition, the second vocal response was never produced during the control trials and therefore always occurred after the dowel had been displaced.

Vocal responses related to initial illumination of the dowel had latencies (VRT1) in the range of 380–400 ms. Vocal reaction times to the dowel shift (VRT2) were in the range of 420 ms. This longer duration of VRT2, though not statistically significant, was consistently observed. It cannot be explained by a possible refractory period following the first vocal response, because the same delay was observed for VRT2 in control experiment 4, where only the second vocal response was produced. Another possible explanation for this difference is that VRT1 corresponded to responses to an expected stimulus, whereas VRT2 corresponded to responses produced in a randomized situation where the stimulus was unexpected.

The most intriguing result of the present experiments was the difference between the early motor response and the much later vocal response following the perturbation. This difference amounted to 315 ms on average. There are a number of points that must be discussed before this temporal dissociation can be considered further. First, we are comparing the latency of an early event in the motor sequence that leads to the correction of hand trajectory (the change in acceleration) with a late event in the vocal response (the voice onset time). Obviously voice onset is preceded by neuromotor events within the vocal tract, the monitoring of which would provide a shorter estimate of the vocal response. However, the speech system is known to have very short intrinsic delays, as shown by the high rate at which speech sounds can be produced. A conservative estimate of the delay between onset of muscle contraction at the level of speech articulators and voice onset may range between 30 and 50 ms (*see* Gracco and Abbs, 1987).

Another point to be discussed is interference between mechanisms responsible for the two simultaneous responses. It is a possibility that, if such an interference had occurred, priority could have been given to the motor task, hence resulting in delaying the vocal response. Let us consider first the possibility of an interaction between the reaching movement directed to the first dowel and the first vocal response. Control experiments 2 and 5 showed that VRT1 did not differ whether vocal responses were performed alone or in association with reaching movements. Reciprocally, control experiments 1 and 3 showed that the motor responses were not influenced by whether the vocal responses were given or not. Reaction times, kinematics and variability of reaching movements recorded in the baseline condition, without vocal responses, were virtually identical with those recorded during the dual task. It remains that the correlation study performed in the main experiment revealed a significant degree of co-variation between MRTs and VRT1s, hence suggesting that the two responses interacted at some level. VRT1s were systematically longer (by about 60–70 ms) than the corresponding MRTs, a difference which held in all conditions. A similar precession of VRT by MRT was reported by Holender (1980) in a situation of concomitant manual and verbal identification of letters: subjects had to press manually a different key for each presented letter, and to pronounce the name of that letter. The vocal response was delayed with respect to the motor response by 150–200 ms. A similar result was obtained by Levelt *et al.* (1985) with an even longer delay (300 ms). There are major differences, however, between these experiments and ours, which may explain the longer MRT-VRT delays observed by these authors. In their experiments the two responses related to overt identification of the same aspect of the stimulus. In addition, the vocal response had a meaningful verbal content. These conditions produced interference between the motor and the perceptual systems, because the two processors competed for a common processing capacity pool, at the disadvantage of the vocal response. In our case, by contrast, the interaction between responses was minimized, because the vocal response had no verbal content, and the two responses answered different questions about the same stimulus. In support of this reasoning, not only were the two responses mutually unaffected by each other (as shown by the results of control experiments 1, 2, 3 and 5), but also (unlike in the MRT-VRT1 case) no correlation was found between the time of occurrence of TPA or TPV and VRT2. This strongly suggests that the two responses were generated independently of each other.

It may be interesting to speculate on why a temporal dissociation between the motor and the vocal responses (as experienced by the subjects and confirmed by the TPA-VRT2 difference) appeared only in the correction situation, and not in the normal situation. The major difference between the results obtained in the two situations is the time to produce the motor response. In the normal situation, where the object remained stationary, it took almost as long to produce the motor response as it took to produce the vocal response. By contrast, in the correction situation this time was greatly reduced. It may be that the strong time pressure under which the second movement was executed gated the activation of fast visuomotor pathways. Alstermark *et al.* (1990) using a similar situation in the cat, reported motor corrections within about 70 ms. They came to the conclusion that such a short delay could only be attained by subcortical pathways. This suggests that the time needed for generating a motor response may change as a function of the context in which the response is given, although the time to signal awareness would remain invariant.

This reasoning is supported by recent results obtained in another experiment where motor and vocal responses were compared (Castiello and Jeannerod, 1991). In this experiment, perturbations in object size rather than in object position were produced using an apparatus described by Paulignan *et al.* (1991*b*). Two dowels which could be illuminated from below by computer controlled light-emitting diodes (a small dowel, 1.5 cm in diameter, surrounded by a larger one, 6 cm in diameter) were presented at the same location. Perturbations of dowel size (e.g. increase in size by shifting the illumination from the small to the large dowel) were randomly produced at the onset of prehension movements. Kinematic analysis revealed that no sign of motor correction could be seen before about 300 ms following this perturbation. The first sign was that the peak deceleration of the transport component occurred earlier in perturbed than in control trials. In addition, the pattern of finger grip formation was modified. The closure of the finger grip around the small dowel was interrupted and finger movements were reverted in order to accommodate for the size of the larger dowel. This reversal occurred around 330 ms following the perturbation. Slower motor response to size perturbations may relate to the higher degree of complexity of the visuomotor pathways for controlling distal movements. This pathway involves processing the visual attributes of objects which are normally used for object identification and recognition. Such processing, which seems to involve cortical mechanisms (e.g. Jeannerod, 1986), would probably be time consuming, and would be compatible with the observed correction delay of more than 300 ms. By contrast, as outlined above, the pathway for processing spatial localization and controlling proximal movements would be simpler and have a shorter time constant.

In the experiment of Castiello and Jeannerod (1991), vocal responses signalling the subjects' awareness of changes in object size kept approximately the same delay as in the present experiment (mean VRT2 was 424 ms, to be compared with the mean value of 420 ms observed in the present experiment). The temporal difference between the motor and the vocal responses was therefore much less than in perturbations in object position. This finding of an invariant delay for subjects to become aware of a visual event is consistent with the notion that access to awareness is a time-consuming process. This notion has been stressed in a slightly different context by the experiments of Libet and his co-workers. They asked subjects to voluntarily flex their wrist or finger and to indicate the time at which they felt the urge or desire to do so, by reporting the clock position of a revolving spot. Simultaneously, slow negative potentials related to movement preparation (readiness potentials, Kornhuber and Deecke, 1965), were recorded through scalp electrodes. The result was that the readiness potential related to the voluntary movement came about 400 ms before the subjects signalled their conscious decision to move (Libet *et al.*, 1983; Libet, 1985).

The results from the present experiment as well as those of Libet and his co-workers therefore stress the fact that neural activity, whether it relates to external events (a visual stimulus) or to internal events (the preparation of a movement), must be processed during a significant amount of time before it can give rise to conscious experience. Whether this duration corresponds to the type of processing to which event-related neural activity is subjected, or to the pathway where this processing occurs, is a matter of speculation (Jeannerod, 1990). It remains, however, that other experimental results reported in the literature could be reinterpreted within this framework. In the experiments of Goodale *et al.* (1986), for example, it might be that awareness of the stimulus change was never achieved because the threshold of the awareness pathway was never reached. The reason for this was that in their experiments, the change in stimulus position occurred during the maximum velocity of the saccade, at a time where foveal vision is known to be 'suppressed' or at least severely degraded. This may also be the case in the Meeres and Graves (1990) experiment. Finally, in pathological situations, where the high-level processing channel is altered by a lesion (like in blindsight patients), only the motor responses can be given and the visual events which trigger them never reach consciousness.

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REFERENCES

ALSTERMARK B, GORSKA T, LUNDBERG A, PETTERSSON L-G (1990) Integration in descending motor pathways controlling the forelimb in the cat: 16. Visually guided switching of target-reaching. *Experimental Brain Research*, **80**, 1–11.

BRIDGEMAN B, LEWIS S, HEIT G, NAGLE M (1979) Relation between cognitive and motor-oriented systems of visual position perception. *Journal of Experimental Psychology: Human Perception and Performance*, **5**, 692–700.

CASTIELLO U, JEANNEROD M (1991) Measuring time to awareness. *Neuroreport*. In press.

CRAGO PE, HOUK JC, HASAN Z (1976) Regulatory actions of human stretch reflex. *Journal of Neurophysiology*, **39**, 925–935.

GEORGOPOULOS AP, KALASKA JF, MASSEY JT (1981) Spatial trajectories and reaction times of aimed movements: effects of practice, uncertainty, and change in target location. *Journal of Neurophysiology*, **46**, 725–743.

GOODALE MA, PELISSON D, PRABLANC C (1986) Large adjustments in visually guided reaching do not depend on vision of the hand or perception of target displacement. *Nature, London*, **320**, 748–750.

GRACCO VL, ABBS JH (1987) Programming and execution processes of speech movement control. Potential neural correlates. In: *Motor and Sensory Processes of Language*. Edited by E. Keller and M. Godnik Hillsdale, NJ: Lawrence Erlbaum, pp. 163–201.

HOLENDER D (1980) Interference between a vocal and a manual response to the same stimulus. In: *Tutorials in Motor Behavior*. Edited by G. E. Stelmach and J. Requin. Amsterdam: North-Holland, pp. 421–431.

JEANNEROD M (1986) The formation of finger grip during prehension. A cortically mediated visuomotor pattern. *Behavioural Brain Research*, **19**, 99–116.

JEANNEROD M (1990) Traitement conscient et inconscient de l'information perceptive *Revue Internationale de Psychopathologie*, **1**, 13–34.

KEELE SW (1973) *Attention and Human Performance*. Pacific Palisades, CA: Goodyear.

KERR B (1973) Processing demands during mental operations. *Memory and Cognition*, **1**, 401–412.

KORNHUBER HH, DEECKE L (1965) Hirnpotentialänderungen bei Willkürbewegungen und passiven Bewegungen des Menschen: Bereitschaftspotential und reafferente Potentiale. *Pflügers Archiv für Gesamte Physiologie*, **284**, 1–17.

LEVELT WJM, RICHARDSON G, LA HEIJ W (1985) Pointing and voicing in deictic expressions. *Journal of Memory and Language*, **24**, 133–164.

LIBET B (1985) Unconscious cerebral initiative and the role of conscious will in voluntary action. *Behavioral and Brain Sciences*, **8**, 529–566.

LIBET B, GLEASON CA, WRIGHT EW, PEARL DK (1983) Time of conscious intention to act in relation to onset of cerebral activity (readiness-potential): the unconscious initiation of a freely voluntary act. *Brain*, **106**, 623–642.

MEERES SL, GRAVES RE (1990) Localization of unseen visual stimuli by humans with normal vision. *Neuropsychologia*, **28**, 1231–1237.

NAPIER JR (1956) The prehensile movements of the human hand. *Journal of Bone and Joint Surgery*, **38B**, 902–913.

PAULIGNAN Y, MACKENZIE C, MARTENIUK R, JEANNEROD M (1990) The coupling of arm and finger movements during prehension. *Experimental Brain Research*, **79**, 431–435.

PAULIGNAN Y, MACKENZIE C, MARTENIUK R, JEANNEROD M (1991*a*) Selective perturbation of visual input during prehension movements: 1. The effects of changing object position. *Experimental Brain Research*, **83**, 502–512.

PAULIGNAN Y, JEANNEROD M, MACKENZIE C, MARTENIUK R (1991*b*) Selective perturbation of visual input during prehension movements. 2. The effects of changing object size. *Experimental Brain Research*. In press.

PERENIN MT, JEANNEROD M (1978) Visual function within the hemianopic field following early cerebral hemidecortication in man–1. Spatial localization. *Neuropsychologia*, **16**, 1–13.

POSNER MI, BOIES SJ (1971) Components of attention. *Psychological Review*, **78**, 391–408.

SKAVENSKI AA, HANSEN RM (1978) Role of eye position information in visual space perception. In: *Eye Movements and the Higher Psychological Functions*. Edited by J. W. Senders, D. F. Fisher and R. A. Monty. Hillsdale, NJ: Lawrence Erlbaum, pp. 15–34.

STARK L, BRIDGEMAN B (1983) Role of corollary discharge in space constancy. *Perception and Psychophysics*, **34**, 371–380.

TAYLOR JL, MCCLOSKEY DI (1990) Triggering of preprogrammed movements as reactions to masked stimuli. *Journal of Neurophysiology*, **63**, 439–446.

WEISKRANTZ L, WARRINGTON EK, SANDERS MD, MARSHALL J (1974) Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain*, **97**, 709–728.

ZELAZNIK HN, HAWKINS B, KISSELBURG HL (1983) Rapid visual feedback processing in single-aiming movements. *Journal of Motor Behavior*, **15**, 217–236.

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NEUROPSYCHOLOGICAL CORRELATES OF STEREOTACTIC SUBCAUDATE TRACTOTOMY

A PROSPECTIVE STUDY

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SUMMARY

Stereotactic subcaudate tractotomy is a surgical procedure performed for the alleviation of intractable affective disorders. It involves the destruction of bifrontal pathways located beneath and in front of the head of the caudate nucleus. We report the first prospective study of the neuropsychological correlates of this operation in 23 patients. Tests of general intelligence, speed and attention, as well as a wide range of focal cognitive tests, including tasks which have been reported in the literature to be sensitive to frontal lobe dysfunction, were administered 1 wk before the operation, 2 wks after the operation and approximately 6 mths after the operation. The results indicated that this operation does not cause any significant, long-term adverse, cognitive deficits. In the post-operative assessment, however, patients show a significant deterioration in their performance on recognition memory tests and a large proportion of them present with a marked tendency to confabulate on recall tasks. In addition, their performance on some of the tasks which are considered to be sensitive to frontal lobe dysfunction is found to be significantly impaired. These deficits are interpreted to reflect frontal lobe dysfunction due to widespread post-operative oedema rather than damage to the subcaudate pathways. The potential for research on these transient effects of the operation for the advancement of our understanding of frontal lobe functions is discussed.

INTRODUCTION

Contemporary psychosurgery may be defined as the neurosurgical treatment of certain psychiatric disorders by means of localized lesions placed in specific brain sites (Bartlett and Bridges, 1977; Valenstein, 1980). In clinical practice the term seems to have been used rather vaguely to refer to a wide variety of neurosurgical techniques targetting different parts of the brain in heterogeneous populations of psychiatric patients, with variable results (Joschko, 1986). In Britain, psychosurgical operations are performed rarely now and usually in patients suffering severe and intractable affective disorders (Poynton *et al.*, 1988).

The operation of stereotactic subcaudate tractotomy (SST) was developed by Knight (1965). He proposed that the subcaudate area offered an opportunity to form a small lesion which might have marked therapeutic effects whilst reducing the adverse sequelae from earlier forms of psychosurgery, including post-operative epilepsy and severe cognitive and personality deficits. This operation involves the insertion into the brain

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of radioactive yttrium rods which destroy bifrontal nerve pathways located just beneath and in front of the head of the caudate nucleus (Newcombe, 1975). It has been reported to be effective with complete recovery or marked psychological improvement in 50–60% of patients who had severe depressive, anxiety or obsessional disorders (Göktepe *et al.*, 1975). To date there has been no comprehensive study of the neuropsychological correlates of SST. Where cognitive variables have been discussed in the past, these were generally limited to measures of global intelligence such as WAIS IQ scores (Bridges, 1973). However, it has long been established that patients with frontal lobe lesions may perform well on general ability tests but their performance on certain specific tasks may be impaired (Milner, 1964; Stuss and Benson, 1986).

There are ethical and scientific reasons which require that the lack of systematic neuropsychological research in this area should be rectified. From an ethical point of view, an operation which involves the irrevocable destruction of brain tissue needs to be comprehensively and continuously evaluated with the most sophisticated techniques available at the time. From a scientific standpoint, neuropsychological research in this area could provide a unique opportunity in the study of brain-behaviour relationships.

Neuropsychological knowledge is heavily reliant upon 'nature's experiments' of brain damage resulting from different types of disease or externally caused trauma. Such haphazard lesions tend to involve relatively wide areas of brain tissue and consequently a large number of patients may be needed in order to delineate specific brain-behaviour relationships. By comparison, SST is a precise type of surgery involving relatively circumscribed and well-defined lesions. Although its target site depends on measurements taken from bony landmarks and the ventricular outline, which may vary from one brain to another, the precise location of yttrium rods varies only very little from patient to patient (Corsellis and Jack, 1973; Newcombe, 1975). In addition, and unlike patients who become impaired because of trauma or disease, those undergoing SST can be studied prospectively. It could therefore be argued that SST provides a rare opportunity for the study of functions of frontal lobe areas involved in this type of operation.

One of the major criticisms of previous research on psychosurgery has been that the vast majority of the reported studies have employed an inadequate experimental design. The fact that suitable control groups have not been used has been particularly criticized (O'Callaghan and Carroll, 1982), in spite of pertinent ethical objections to such controls. In studying the cognitive correlates of SST (as opposed to its efficacy in alleviating psychiatric symptoms) it is also difficult to envisage appropriate comparable groups. Although patients undergoing this operation usually have a diagnosis of resistant affective disorder, they are not homogeneous in other respects, for example, in terms of age, number of previous episodes and length of present illness, current symptoms and pre-operative psychopharmacological treatment. Furthermore, only a limited number of patients undergo this operation each year and they are highly selected, not only in terms of being involved in a tertiary referral, but also in having consented to such a treatment (Poynton *et al.*, 1988). It would appear not possible to find another group of patients who could be suitably matched to take these factors into account and, therefore, a prospective study in which patients are used as their own controls would seem a more appropriate approach than a between-subjects experimental design.

We report a prospective study of SST. Our aim has been to investigate potential neuropsychological changes associated with this operation. In addition, we have been aiming to study possible correlations between cognitive and psychiatric changes in the patients undergoing this operation. Tests which are known to be sensitive to frontal lobe dysfunction, as well as tests of general intelligence, memory, language, visuospatial analysis and attention were administered before the operation, soon after the operation and 6 mths following the operation. Psychiatric assessments were carried out at the same intervals. A full clinical description of the patients and the results of repeated systematic psychiatric assessments will be reported separately (Poynton, unpublished).

METHODS

Subjects

Initially we aimed to assess 20 consecutive patients but had to include 3 more, in order to compensate for a corresponding number of patients who were not available for 6-mth assessments. Amongst the 23 patients, 8 were men and 15 women with mean age 49 yrs (range 21–74 yrs). In accordance with Research Diagnostic Criteria (RDC) (Spitzer *et al.*, 1978), 16 patients presented with major depressive disorder, 5 patients had bipolar disorder (including bipolar I and bipolar II), 1 patient had a phobic disorder and another presented with major depressive disorder and obsessive compulsive disorder. All illnesses were chronic and resistant to treatment with a mean duration of current episode of illness of 64.6 mths (range 0–144 mths). Prior to their admission to the Brook Hospital for operation, 12 patients were at home and 11 were psychiatric in-patients. After the operation most patients were discharged from the neurosurgical unit to their local hospital at between 2 and 4 wks. The mean length of subsequent hospital stay was 2.1 mths (range 0–6 mths).

Preliminary procedures

Patients were referred by their own consultant psychiatrist and selected for operation by the consultant psychiatrist (P.K.B.) and the consultant neurosurgeon (J.R.B) at the Geoffrey Knight Unit for Affective Disorders, Brook Hospital. The criteria for offering SST were: (*a*) diagnosis of unipolar depression, bipolar affective disorder, obsessive compulsive disorder or anxiety state; (*b*) the disorder had been unresponsive to all other alternative treatments. The nature of the operation, together with potential benefits and risks were discussed both with the patients and their relatives. If a patient decided to take up the offer for surgery, it was then necessary for him or her to see a panel of 3 Mental Health Commissioners who must by law give approval for psychosurgery, under Section 57 of the Mental Health Act, 1983. These commissioners are appointed by the Secretary of Health and consist of a consultant psychiatrist, a lawyer and a layman. The consultant psychiatrist must assess a patient's suitability for operation and all 3 commissioners assess consent for surgery (for a more detailed account, *see* Poynton *et al.*, 1988).

The patients were admitted approximately 2 wks prior to the scheduled operation. They had a full physical examination and appropriate screening tests including CT scans, with the exception of 1 patient, who had an MRI instead. The scans were assessed by the senior radiologist of the hospital and the degree of sulcal enlargement and ventricular size were rated on 0–3 scales (0 denoting normal scan and 3 highly abnormal). No clinically significant abnormalities in the CT scans were found (*see* Table 1).

Prior to operation most patients continued to have some psychotropic medication, i.e. antidepressant with or without neuroleptic drugs.

TABLE 1. SUMMARY OF THE CT SCANS IN 22 PATIENTS

	Sulcal enlargement	*Ventricular enlargement*
None	15	16
Mild abnormality	7	6
Moderate abnormality	0	0
Severe abnormality	0	0

Operation

The surgical lesion in SST involves relatively small areas of the frontal lobes. With the patient under general anaesthesia lesions are produced by implants of yttrium placed stereotactically in the basofrontal aspects of the frontal lobes (Fig. 1).

Following the operation patients usually remain in bed for about 24 h and their pre-operative medication is continued. There are few obvious immediate adverse effects of the operation, although some patients may suffer from headache which is usually relieved with mild analgesics such as paracetamol. Very occasionally patients may suffer a period of clinically apparent confusion due to induced oedema and this confusion may last from 1 wk up to 2 mths. The occurrence of oedema post-operatively has been recognized clinically for several years. Its presence at 2 wks post-operatively was confirmed in Magnetic Resonance Imaging (MRI) scans performed in 2 of our patients. Subsequent MRI scans on the same patients indicated that the oedema has disappeared at a 6-mth follow up. Illustration of this phenomenon is presented in Fig. 2 consisting of more recent and better-quality scans of 2 patients not included in the present study (Malitzia, personal communication). It has been established that the oedema is widespread, involving the upper parts of the frontal lobes and may extend to the anterior poles of the temporal lobes. The extent of the oedema, however, has been found to vary from patient to patient (Malitzia, personal communication).

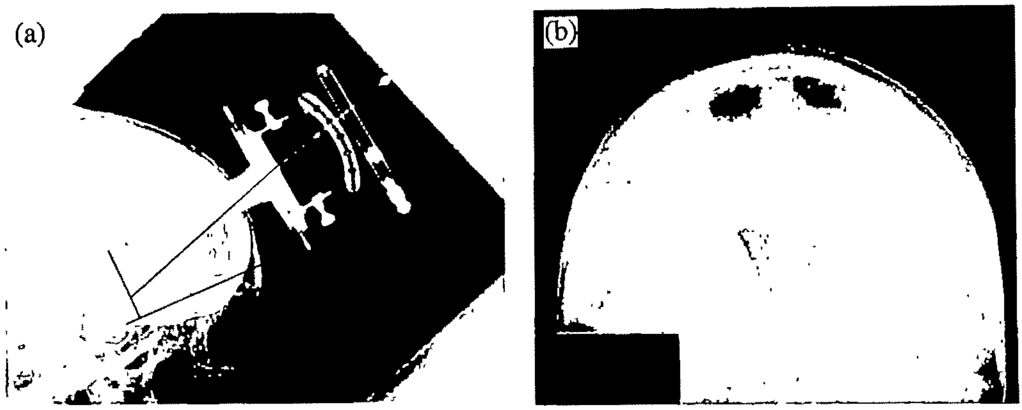

FIG. 1. The McCaul stereotactic device *in situ* with lines indicating the path of insertion of yttrium rods and the landmarks used to determine this (a); yttrium rods *in situ* post-operatively (b).

Assessments

In addition to detailed psychiatric interviews using observer-rated scales, the patients' mood and other aspects of their psychological state were monitored with self-rating scales (if, that is, patients were able to cooperate) (Poynton, unpublished).

In parallel with the psychiatric assessments neuropsychological studies were performed on three occasions. The first was carried out 6–9 d prior to the operation (pre-operative assessment); the second, 2 wks after the operation (post-operative assessment); the third, approximately 6 mths after the operation (follow-up assessment). For the majority of patients, the pre-operative assessment was performed in two sessions. However, for some patients this was not feasible because they were severely depressed, agitated or fatigued and a third session was required in order to enable them to perform as near their optimal level as possible For each post-operative and follow-up assessment only 1 session was needed.

Tests

A comprehensive battery of neuropsychological tests was employed. This included (*a*) tests of general intelligence; (*b*) tests of memory; (*c*) tests which are thought to be sensitive to frontal lobe dysfunction; (*d*) non-frontal focal cognitive tests; (*e*) tests of speed and attention.

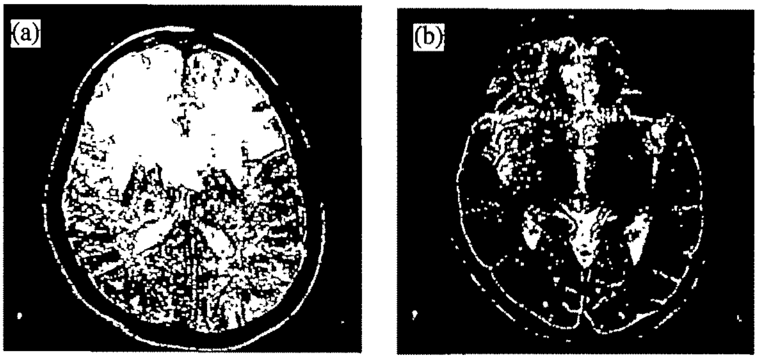

FIG. 2. MRI scans of 2 different patients. 2 wks after the operation indicating widespread oedema (a); 6 mths after the operation with the oedema resolved (b).

In the pre-operative assessments, the complete battery of tests was administered. The same tests were given in the follow-up assessments except the National Adult Reading Test (this test gives a measure of pre-morbid ability which, by definition, is not subject to changes). The post-operative assessments also included the same tests apart from the National Adult Reading Test and the Wechsler Adult Intelligence Test below (the former for the reason stated above and the latter in order to minimize practice effects). Where possible, alternative forms of the tests were administered in the different assessments. In detail the tests were as follows·

General ability tests

National Adult Reading Test (NART) (Nelson, 1982). This test was used to provide an estimate of optimal, pre-morbid general level of intelligence in terms of IQ equivalents.

Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955). A shortened version of this scale was used. It comprised 4 verbal (Arithmetic, Digit Span, Vocabulary and Similarities) and 3 non-verbal or performance subtests (Picture Completion, Picture Arrangement and Block Design). The results were prorated to yield Verbal, Performance and Full Scale IQs. The discrepancy between the estimated optimal IQs on the NART and obtained WAIS IQs was considered as an index of global intellectual deterioration. As stated above, the WAIS was not included in the post-operative assessment, although the Digit Span subtest was given in all 3 assessments.

Graded Difficulty Arithmetic Test (GDAT) (Jackson and Warrington, 1986). In addition to the Arithmetic subtest of the WAIS, this test was administered. It consists of timed mental calculations (12 additions and 12 subtractions), the time-limit for each calculation in this study being extended to 20 s. The score each patient obtained represented the number of calculations that he/she performed correctly.

Advanced Progressive Matrices (APM), Set 1 (Raven, 1958). This is a set of non-verbal reasoning problems. Both the number of problems completed correctly and the corresponding age-scaled scores with a mean of 10 were used as measures of performance. These two measures did not yield significantly different results and only the latter will be reported. The total time in seconds taken by the patient to complete the task was included as an additional index of performance

Memory tests

Recognition Memory Test (RMT) (Warrington, 1984). The test was administered following the standard procedure. Three independent versions of the test (E. K. Warrington, personal communication) were randomized across sessions for each patient and both raw and age-scaled scores of verbal (RMW) and visual (RMF) recognition memory were obtained. Only the scaled scores with a mean of 10 will be referred to henceforth.

Logical Memory (LM) (Wechsler, 1945). Three stories ('Anna Thompson', 'Liner New York', 'Dogs are trained') were randomized across test sessions for each subject. Each story was given following the standard procedure and both immediate and delayed (30 min) recall memory measures were obtained Scores reflected the number of correct ideas reproduced from each story.

Associate Learning (AL) (Wechsler, 1945). Two sets of paired-word associates were used and randomized for each subject. The set of associates which was given in the pre-operative assessment was also administered in the follow-up assessment. Administration and scoring were performed according to the standard procedure but, in addition to immediate recall, delayed recall measures were obtained.

Tests of frontal lobe dysfunction

Word Fluency (WF). The test required the subject to generate within 90 s as many words as possible starting with a particular letter of the alphabet. Two letters (S and V) were randomized for each subject and the letter which was used in the pre-operative assessment was also used in the follow-up assessment. A patient's score was equivalent to the number of words generated within the time-limit. Since the number of words starting with a particular letter in the language differs significantly, the difficulty of the task is presumably proportional to the frequency of words in the language starting with such a letter. In order to compare the performance of patients across the sessions a formula was devised following the norms on word fluency tests for different letters by Borkowski *et al.* (1967). Accordingly, the number of words generated starting with the letter V was multiplied by 1.95. Additional measures of performance were the number of the errors (inappropriate words to the task) and the number of perseverations (repetition of words).

Modified Card Sorting Test (MCST) (Nelson, 1976). This is a shortened version of the Wisconsin Card Sorting Test (Milner, 1963) and it was administered and scored according to the standard instructions. Four measures were obtained: the number of categories achieved, the number of errors made; the number of perseverations made; the total time in seconds taken by the patient to complete the test.

Cognitive Estimates Test (CET) (Shallice and Evans, 1978). The patient was required to make estimates in response to 10 questions of the kind, 'How fast do race horses gallop?' The estimates were scored according to the normative data, higher scores reflecting worse performance. The total time in seconds required by the patient to complete the test was taken as an additional measure of performance.

The Tower of London Test (TLT) (Shallice, 1982). This test which is based on artificial intelligence problem-solving simulations consists of 12 problems thought to be heavily loaded on planning abilities. Two measures were obtained: the total number of problems completed correctly and the so-called 'planning score' reflecting the speed of performance.

Stroop Colour-Word Interference Test (SCWIT). This was the National Hospital's (Queen Square) version of the Stroop task. It comprises words printed in different colours and the patient was first required to read the words and subsequently to name the colours of the printed material while ignoring the content of the words. Two measures from each part of the test were obtained: the number of errors made; the time needed by the patient to complete it.

Bimanual Coordination Test (BCT) (Luria, 1966). This was a simple hand coordination task in which the patient was asked to reverse simultaneously the positions of hands, one clenched, the other flat on the table. The number of correct alternations within 15 s and the number of errors made provided measures of performance.

Non-frontal focal cognitive tests

Graded Naming Test (GNT) (McKenna and Warrington, 1983). The test consists of 30 line drawings and it was administered following standardized procedures. The number of items named correctly yielded a measure of naming skill and this number was transformed into a scaled score with a mean of 10. Only scaled scores will be referred to below.

Token Test (TT) (Coughlan and Warrington, 1978). This was a shortened version of the test of abstract sentence comprehension devised by De Renzi and Vignolo (1962). The patient was given a score corresponding to the number of responses (out of 15) completed correctly.

Position Discrimination or Dot Centre Test (DC) (Warrington and James, 1988). This is a test of visuospatial analysis requiring the subject to identify which of two squares has a dot exactly in its centre. There are 20 trials and each patient was given a score corresponding to the number of correct responses.

Sequential Unilateral Hand Movements (SUHM). This type of task is considered to be sensitive to apraxic difficulties (Kimura, 1977). The patient was asked to copy a 3-step movement, first with the right (SUHMR) and then the left (SUHML) hand. The number of correctly completed movements within 15 s and the errors counted yielded measures of the patient's performance.

Tests of attention and speed

Digit Symbol Test (DST). This is a subtest of the WAIS involving symbol substitution and each patient was given an age-related scaled score.

Trail Making Test (TMT) (Lezak, 1976). Originally part of the Army Individual Test Battery (1944), this task requires the subject to connect consecutively with a continuous line numbers dispersed on a sheet (Part I), and then numbers and letters of the alphabet while alternating between these two types of stimuli (Part II). The time taken to complete each part and the number of errors made by the patient were used as measures of performance

Mental Speed Tests (MST) (Willison, 1988). Four tests of this battery were used and they included. Counting Backwards (CB) from 30 to 1; Number Naming (NN); Colour Patch Naming (CPN); and Digit Cancellation ('O') (DCan). The measures of performance used were the time taken by the patient to complete each test and the numbers of errors made.

RESULTS

General ability tests

All data were analysed using the Statistical Package for the Social Sciences (Nie *et al.*, 1975) (SPSS) computer programs. The means and standard deviations of the scores in the 3 assessments are shown in Table 2. (Some of the patients were unable to complete certain tests, particularly in the first 2 assessments. This has been taken into account in all statistical analyses using the facility of SPSS by which cases with missing values were deleted on a test-by-test basis. The number of patients completing individual tests on which significant changes were found are specified below.) There is an approximately 10-point discrepancy between the mean values of the estimated optimal NART and obtained WAIS Full-Scale IQs in the pre-operative and follow-up assessments. Considering individual cases in the pre-operative assessment, 9 out of 23 patients (39%) showed a 12-point or greater discrepancy between optimal and obtained IQs. A chi-square test indicated that the observed proportion of patients with such a discrepancy is significantly greater ($\chi^2 = 8.2$, $P < 0.01$) than the expected one (4%) in the general population (Nelson, 1982). The IQ scores of individual patients were virtually unchanged at the follow-up assessment and in no case was there a significant IQ discrepancy between optimal and obtained IQs that had not been present pre-operatively.

TABLE 2 SUMMARY OF THE MEAN SCORES ON GENERAL ABILITY TESTS AND COMPARISONS OF DATA IN DIFFERENT ASSESSMENTS BY WILCOXON TESTS FOR REPEATED MEASURES

	Pre-op.	*Post-op.*	*Follow-up*
NART IQ	111.3 (4.9)	–	–
WAIS Verbal IQ	106.0 (10.1)	–	105.2 (10.2)
WAIS Performance IQ	95.5 (11.8)	–	97.7 (13.3)
WAIS Full-Scale IQ	101.6 (9.8)	–	102.1 (9.2)
Digit Span	10.6 (3.1)	10.4 (3.5)	10.8 (2.7)
GAT	13.2 (5.7)	11.8 (6.0)	13.6 (5.5)
AM	7.7 (3.2)	7.0 (3.6)	9.5 (2.9)
AM time	299.7 (139.1)	267.3 (154.6)	259.7 (104.2)

SD in brackets.

The patterns of the mean subtest scores on the WAIS in the pre-operative and follow-up assessments were unremarkable. The Digit Span subtest scores in all 3 assessments were at an average level.

The scores of the patients on different general ability tests in the 3 sessions were compared with Wilcoxon (two-tailed) tests for repeated measures. Specifically, the pre-operative data were first contrasted with those in the post-operative assessment and then with those in the follow-up assessment (Wilcoxon tests for repeated measures were also used for comparing the scores of the patients in different assessments on both focal cognitive and speed tests below). Because of the large number of comparisons in the study, results in tests yielding a level of significance equal to, or greater than, $P = 0.01$ were deemed non-significant. There were no statistically significant changes on tests of general ability across the different assessments. However, the patients showed a strong trend of an improvement on Advanced Matrices (AM) in the follow-up assessment ($Z = -2.3$, $n = 15$, $P < 0.02$).

Memory tests

The mean and standard deviations for the memory tests in the 3 assessments appear in Table 3.

TABLE 3 SUMMARY OF THE MEAN SCORES ON MEMORY TESTS AND COMPARISONS OF DATA IN DIFFERENT ASSESSMENTS BY WILCOXON TESTS FOR REPEATED MEASURES

	Pre-op.	*Post-op.*	*Follow-up*
RMW	9.4 (3 1)	6.1 (3 1)**	10.6 (3.1)
RMF	7.4 (3.1)	4.9 (3.2)*	7 6 (3.4)
LM immediate recall	9.8 (4.1)	8.5 (5.3)	8.6 (4 6)
LM delayed recall	7.8 (4.1)	6.7 (5.9)	7.8 (4.5)
PA immediate recall	11.1 (3.4)	10.6 (4.5)	11.0 (4.3)
PA delayed recall	6.8 (1.0)	5.5 (3.2)	6.5 (2.2)

SD in brackets; $^{*}P < 0.01$; $^{**}P < 0.001$; pre-op. vs post-op

A significant deterioration on recognition memory tests was found in the post-operative as compared with pre-operative assessment both for verbal (RMW) ($Z = -3.4$, $n = 20$, $P < 0.001$) and visual (RMF) ($Z = -2.6$, $n = 20$, $P < 0.01$) material. Scores on recall memory tests remained at about the same levels in the 3 assessments. Detailed analysis of the story content of the Logical Memory (LM) tests, however, revealed that post-operatively patients generated a significantly larger number of confabulations than in the other 2 assessments (Table 4). [Confabulation has been defined here as the

TABLE 4. SUMMARY OF NUMBER OF PATIENTS AND THEIR CONFABULATIONS DURING IMMEDIATE AND DELAYED STORY RECALL

	Pre-op.		*Post-op.*		*Follow-up*	
	Immediate	*Delayed*	*Immediate*	*Delayed*	*Immediate*	*Delayed*
Patients confabulating	1	3	10	11	3	4
Total number of confabulations	1	4	20	26	6	5

generation of a completely novel idea or the transposition of ideas within a story resulting in a change of meaning of a passage (Kopelman, 1987)].

Tests of frontal lobe dysfunction

The means and standard deviations of scores on tests of frontal lobe dysfunction are shown in Table 5.

TABLE 5 SUMMARY OF THE MEAN SCORES ON TESTS OF FRONTAL LOBE DYSFUNCTION AND COMPARISONS OF DATA IN DIFFERENT ASSESSMENTS BY WILCOXON TESTS FOR REPEATED MEASURES

	Pre-op.	*Post-op.*	*Follow-up*
WF number of words	20.0 (7.1)	15.7 (8.1)*	20.1 (7.9)
WF perseverations	0.1 (0.2)§	0.6 (0.8)	0.9 (1.4)
MCST categories	4.4 (2.1)	2.0 (1.9)*	4.3 (2.3)
MCST errors	13.5 (7.7)	28.9 (12.6)*	14.8 (9.9)
MCST perseverations	4.1 (5.1)	19.4 (13.7)*	6.3 (7.5)
MCST time	316.6 (181.7)	304.9 (182.7)	319.0 (107.8)
CET score	5.6 (2.7)	9.4 (5.2)	7.2 (4.2)
CET time	164.7 (58.0)	151.7 (81.0)	158.2 (62.5)
TLT number correct	8.6 (1.9)	8.7 (2.1)	9.3 (4.0)
TLT planning score	21.0 (6.7)	20.9 (6.7)	22.5 (7.2)
SCWIT reading time	11.8 (3.6)	13.7 (5.1)	12.7 (4.1)
SCWIT reading errors	0.1 (0.2)§	0.3 (1.5)	0.3 (0.6)
SCWIT colour name time	34.7 (11.6)	62.4 (49.1)	41.3 (28.3)
SCWIT colour name errors	1.1 (1.4)§	4.6 (5.4)	2.7 (4.3)
BCT number correct	11.7 (4.6)	7.3 (5.4)	9.9 (5.1)
BCT errors	0.6 (1.3)§	2.6 (3.7)	0.8 (1.1)

SD in brackets; *$P < 0.01$, pre-op. vs post-op ; § ceiling effects precluded comparisons of scores between different assessments.

Wilcoxon tests showed a significant reduction in the number of words generated on the Word Fluency test (WF) post-operatively ($Z = -2.3$, $n = 17$, $P < 0.01$). Fewer categories were completed on the Modified Card Sorting Tests (MCST) ($Z = -2.7$, $n = 15$, $P < 0.01$), with more errors ($Z = -2.8$, $n = 15$, $P < 0.01$) and perseverative responses ($Z = -2.8$, $n = 15$, $P < 0.01$). The apparent deterioration in the patients' performance on the Cognitive Estimates Test (CET) post-operatively was just outside our criterion of statistical significance ($Z = -2.2$, $n = 16$, $P < 0.02$). The time needed by the subjects to complete a task did not appear to have affected the level of performance in any of these tests.

The mean error score in the Colour Naming part of the Stroop Colour-Word Interference Test (SCWIT) appears substantially increased during the post-operative assessment. Close inspection of the data, however, indicated wide variability in the distribution of scores during this assessment. Seven patients made no errors and the rest made 1 – 18 errors. Similarly, the mean error score on the Bimanual Coordination Test (BCT) appears substantially increased in the post-operative assessment but, again, this is underlied by a wide variability in the distribution of scores. Nine patients made no errors, 1 patient made 15 errors and the rest made from 1 to 8 errors.

Non-frontal focal cognitive tests

The mean scores and standard deviations for these tests appear in Table 6. There were no significant changes in the performance of the patients in the different assessments.

Tests of speed and attention

The mean scores and standard deviations on these tests appear in Table 7.

Apart from an improvement in patients' performance on the Digit Symbol subtest of the WAIS in the follow-up assessment as compared with pre-operative assessment ($Z = -2.6$, $n = 19$, $P < 0.01$), no other significant changes on tests of speed and attention were found. An apparent deterioration in the error score on the Trail Making Test TMT(II) during the post-operative assessment was confounded by a wide variability in the data. Nine patients made no errors and those remaining made 1–10 errors.

TABLE 6. SUMMARY OF MEAN SCORES ON NON-FRONTAL FOCAL TESTS AND COMPARISONS OF DATA IN DIFFERENT ASSESSMENTS BY WILCOXON TESTS FOR REPEATED MEASURES

	Pre-op.	*Post-op.*	*Follow-up*
GNT	11.2 (1.7)	10.5 (2.1)	11.2 (2.0)
TT	13.7 (1.8)	13.1 (2.7)	13.7 (2.0)
DC	18.4 (1.7)	17.7 (1.8)	18.4 (1.0)
SUHMR number correct	5.5 (1.9)	4.6 (2.9)	6.3 (2.5)
SUHMR number of errors	0.2 (0.5)§	0.7 (1.2)	0.5 (0.8)
SUHML number correct	5.9 (1.7)	5.2 (3.1)	6.4 (2.4)
SUHML number of errors	0.2 (0.5)§	0.5 (1.4)	0.3 (0.7)

SD in brackets; § ceiling effects precluded comparisons of scores between different assessments.

TABLE 7. SUMMARY OF MEAN SCORES ON SPEED TESTS AND COMPARISONS OF DATA IN DIFFERENT ASSESSMENTS BY WILCOXON TESTS FOR REPEATED MEASURES

	Pre-op.	*Post-op.*	*Follow-up*
Digit symbol	8.3 (2.5)	8.4 (2.1)	10.0 (2.9)*
TMT(I), time	55.3 (20.6)	74.2 (38.3)	53 8 (26.7)
TMT(I), errors	0	0.2 (0.6)	0
TMT(II), time	124.8 (58.7)	207.2 (200.1)	137.3 (131.0)
TMT(II), errors	0.5 (0.9)	2.1 (2.8)	1 8 (2.8)
CB, scaled score	7.7 (3.1)	7.7 (3.3)	8.5 (3.4)
NN, time	18.7 (9.5)	19.1 (5.1)	17.8 (4.5)
NN, errors	0	0.1 (0.5)	0.1 (0.5)
CPN, time	14.0 (2.2)	17.2 (8.8)	17.7 (11.4)
CPN, errors	0.1 (0.2)§	0.1 (0.6)	0.2 (0.5)
DCan, scaled score	5.8 (3.2)	5.4 (3.3)	7.5 (3.9)
DCan, errors	1.2 (3.5)	0.8 (2.2)	0.5 (1.4)

SD in brackets; *$P < 0.01$, pre-op. vs follow-up, § ceiling effects precluded comparisons of scores between different assessments.

DISCUSSION

We report the first prospective study of neuropsychological correlates of SST. A wide range of tests of general intelligence and focal cognitive function were administered and the scores of the patients prior to their operation were compared with those obtained at 2 wks and 6 mths after the operation. As far as the results on general ability tests are concerned, in the 6-mth follow-up assessment the patients performed as well as before the operation. Indeed, there was a strong trend towards an improvement on a set of non-verbal reasoning problems (Matrices). These findings are in good accord with previous studies suggesting that patients with frontal lobe lesions may not be impaired on tests of general intelligence (Milner, 1964; Stuss and Benson, 1986).

However, this conclusion must be qualified. Unlike any previous study of psychosurgery, measures of optimal levels of general intelligence of the patients were estimated objectively using the National Adult Reading Test. Pre-operatively, as a group, our patients showed a discrepancy between their estimated optimal and obtained IQs suggestive of a mild degree of general intellectual underfunctioning or deterioration. In their follow-up assessment the same degree of discrepancy between optimal and obtained IQs was found to be present. These discrepancies can be interpreted in a number of ways which are not necessarily mutually exclusive. First, it could be argued that the mild degree of underfunctioning prior to the operation was associated with psychological factors (depression and anxiety). At the follow-up assessment similar factors could have also been responsible for the patients' observed inefficiency since a significant proportion of them continued to experience depressive symptoms [this issue will be considered in more detail elsewhere, Poynton *et al.* (personal communication)]. A further study with longer follow-up assessments could clarify this point.

A second possible explanation of the data would be that, whereas pre-operatively psychological factors might have hindered the patients' performance, at the follow-up assessment organic factors were responsible for their underfunctioning, a kind of cognitive 'blunting' induced by the operation. Such cognitive impairment might also be suggested by the fact that they had apparently failed to benefit from practice effects, despite a substantial improvement in their psychological state. However, this interpretation would be difficult to reconcile with the fact that in the follow-up assessment the patients' scores on tests of frontal lobe dysfunction were not significantly different from those they had obtained pre-operatively (frontal lobes being the site of the lesion).

A further possible explanation is that the patients' underfunctioning on general intelligence tests was associated with a mild degree of cortical dysfunction predating the operation. Consistent with this interpretation would be the fact that approximately half of the CT scans of the patients were rated as showing mild atrophic changes. However, closer inspection of the data does not entirely support this view. Assuming that a discrepancy of 12 points or more between estimated and obtained full-scale IQs denotes a significant degree of general intellectual underfunctioning, roughly a half of the patients (4/10) with CT evidence of atrophy presented with such an IQ discrepancy, as compared with just over one-third of those (5/13) without CT evidence of atrophy. It would therefore appear that there is no unequivocal evidence that the patients' mild underfunctioning on general ability tests both before and 6 mths after the operation was associated with either organic or psychological factors or, indeed, both kinds of variables.

To delineate the relative weights of these variables a more focused approach to these effects than the present experimental design would be needed.

With regard to the data on memory tasks, it was established that recall tests (story, paired associates) did not yield statistically significant measures of deterioration in the patients' performance after their operation. However, an interesting finding was that, during story recall in the post-operative assessment, approximately half of the patients produced significantly more confabulations than in either of the other 2 assessments. The fact that confabulations were generated in the absence of any significant decrement in the scores on recall would be consistent with the study of Mercer *et al.* (1977). In this latter study it was suggested that the degree of confabulation is not necessarily closely associated with the severity of memory disturbance and it is more akin to the ability of patients to be self-corrective and monitor their own behaviour. Our patients were indeed impaired in this regard as suggested by their unsatisfactory performance on the Modified Card Sorting Test (*see below*). It should perhaps be added that the present results are also in keeping with the literature suggesting that a crucial element in the pathogenesis of confabulation is frontal lobe dysfunction (for a review *see* Stuss and Benson, 1986).

The recognition memory tests proved particularly sensitive to the post-operative effects, resulting in significantly impaired scores for both verbal and visual material. In the follow-up assessment the scores of the patients returned to the same levels as pre-operatively, suggesting no long-term recognition memory impairment.

The discrepancy between the patients' level of performance on recall as compared with recognition memory tests post-operatively deserves further consideration. Although numerous types of dissociation in aspects of memory have been clearly established in the literature, e.g. between long-term and short-term memory, or between verbal and non-verbal/modality specific deficits, or between episodic and semantic memory impairments (*see* e.g. Shallice, 1988), until recently there have been no claims of dissociation between processes in memory retrieval, one involving recall and the other recognition. Furthermore, it has been argued that recognition is 'superior' to recall (Hirst *et al.*, 1986), suggesting that both types of memory task involve the same processes and that recognition is easier to perform than recall (Delbecq-Derouesné *et al.*, 1990). Our data on memory tests indicate that while our patients' performance on recall tests post-operatively was comparable with their performance on equivalent tasks pre-operatively and within the normal range (confabulations notwithstanding), on alternative forms of the recognition tests their scores were within the range of amnesic patients (Perani *et al.*, 1991). This discrepant pattern is comparable with the findings of a single case study by Delbecq-Derouesné *et al.* (1990). They described a patient who, following an aneurysm of the anterior communicating artery, presented with a large area of hypodensity affecting the internal parts of both frontal lobes. On testing, he produced normal responses on tasks of recall but his performance on recognition tasks was at the same level as that of amnesic patients. This dissociation was discussed in the context of models of normal memory and it was argued that the observed recognition defect was due to an impairment at the retrieval stage rather than in the initial processing of material to be remembered or in the storage stages of the memorization process. Like many of our patients, this patient was also prone to confabulating. The present study therefore appears to provide further evidence indicating that not only the pathogenesis of confabulation but also a dissociation between relatively well preserved recall and impaired recognition memory processes are associated with frontal lobe dysfunction.

One more aspect of the memory data is noteworthy. The scores of the patients on the visual recognition memory tests was at a low average level both pre-operatively and in the follow-up assessment, suggesting a long-term inefficiency. This finding parallels the mild degree of their underfunctioning on general intelligence tests as discussed above and for its interpretation we would be inclined to use the same arguments. However, although the recognition memory tests have been found to be sensitive in differentiating known organic disorders from depression ('substantially' depressed patients performing not significantly differently from control subjects), a small but significant negative correlation has also been reported between scores obtained on the visual recognition memory test and degree of depression (Coughlan and Hollows, 1984). It would therefore be reasonable to argue that the inefficiency of our patients on the visual recognition memory tests in the pre-operative and follow-up assessments was primarily associated with their depression. Such an interpretation would be consistent with the notion that depression is associated with a right hemisphere dysfunction (Flor-Henry, 1969, 1984) and the well-established fact that visual memory is also subserved by the right hemisphere (e.g. Milner, 1966; Warrington, 1984).

We have used several tests which have been reported in the literature to be sensitive to frontal lobe dysfunction and the results were variable. There was evidence of a significant deterioration in the patients' performance post-operatively on word fluency tests and the Modified Card Sorting Test. Reduced performance on word fluency tests in non-dysphasic patients with frontal lobe lesions was first demonstrated by Milner (1964). According to Milner's work, the principal locus of the deficit is anterior to Broca's area, in the orbital cortex, although patients with lesions in the central face area may show an even greater defect. However, patients with lesions in the right orbital frontal region may also be impaired on verbal fluency tasks. Subsequent investigations were broadly consistent with these early findings of reduced word fluency in patients with frontal lobe lesions (e.g. Benton, 1968; Miller, 1984). Word fluency tests have also been found to discriminate fairly accurately patients with frontal lesions from patients with non-frontal brain-impaired or psychiatric patients (Crockett *et al.*, 1986).

The deterioration in the performance of the patients on the Modified Card Sorting Test was perhaps more dramatic and observed in all measures we have recorded. Thus, patients achieved fewer categories on this sorting task and made more errors, particularly perseverative errors, post-operatively than pre-operatively. These observations are in accord with previous studies indicating that sorting tasks are very sensitive to frontal lobe dysfunction (Milner, 1963; Nelson, 1976). Although in Milner's work the principal locus of deficit appears to be around Broadman's area 9 in the left hemisphere, other parts of the frontal lobes may also elicit significant deficits.

There was also a strong trend of deterioration in the patients' performance on the Cognitive Estimates Tests in the post-operative phase. Shallice and Evans (1978) found that this kind of task is sensitive to frontal lobe lesions and we would argue that our result goes some way in supporting this notion. Shallice and Evans, however, did not attempt to differentiate the sensitivity of the test to different areas of the frontal lobes (*see below*).

It is important to note that the deterioration in the patients' performance on the above frontal lobe tests post-operatively was observed in the context of a lack of deterioration on certain general ability tests (*see* Table 2). Similarly, there was no evidence of any significant change in the patients' performance on a series of other, non-frontal, focal cognitive tests, nor on tests of speed (*see below*).

The specificity of the aforementioned tests merits further consideration. One issue concerns the precise anatomical correlates of their apparent sensitivity of frontal lobe dysfunction. In our view, the term 'frontal lobe dysfunction' is overinclusive since research suggests that distinct types of impairment may be determined by the locus and laterality of a frontal lobe lesion and the extent to which subcortical pathways are involved. Thus, for example, it has been argued that bilateral anterior brain damage, with evidence of involvement of the mesial and inferior orbital aspects of the frontal lobes or their connections, gives rise to affective changes whereas impairments in high level cognitive activity follows dorsolateral lesions (Damasio, 1985; Kolb and Wishaw, 1990). However, to date, and as indicated above, the specific loci of sensitivity of tests of frontal lobe dysfunction remains rather ill defined. The present study provides limited clarification in this regard. As seen in Fig. 2, post-operatively, MRI shows widespread bilateral oedema in the frontal lobes which extends well into their lateral aspects. Since the above tests produced impaired performance during the post-operative phase only, it may be concluded that these tests do not reflect permanent dysfunction resulting from tissue destruction but they reflect a transient process in which aspects of functioning of the frontal lobes are disturbed by oedema. Whilst it could be argued that the return of the patients' performance to pre-operative levels during the follow-up assessment might result from practice effects (the same frontal lobe tests were administered in all 3 assessments), this seems unlikely to account for a deterioration over a short period and a return to previous levels after a much longer interval. For further clarification a future study might attempt to investigate and compare the levels of performance of different patients at different stages after the operation, possibly including concurrent monitoring with MRI, thus allowing correlations between the extent of oedema and degree of integrity of cognitive skills.

The remaining tests considered to be as sensitive to frontal lobe dysfunction did not yield statistically significant changes in the patients' performance post-operatively. Both the Stroop Colour-Word Interference Test and the Bimanual Coordination Test produced trends of deterioration in the patients' performance post-operatively. However, there was wide variability in the scores of the patients suggesting that the sensitivity of these tests to frontal lobe dysfunction may depend on factors which were not studied, such as the severity of oedema of the frontal lobes in our patients.

All the tests designated as 'non-frontal focal', as well as a range of tests of speed and attention, failed to produce significant changes in the post-operative and follow-up assessments with the exception of Digit Symbol. On this latter test patients obtained higher scores in the follow-up than pre-operative assessment and this result very probably reflects an improvement in the patients' psychomotor state 6 mths after their operation.

In conclusion, the present study indicates that SST does not cause any significant, long-term, adverse cognitive deficits. Post-operatively, however, a transient deterioration in the patients' performance on certain tests which are sensitive to frontal lobe dysfunction is observed. In the post-operative phase recognition memory functions also become impaired and a large proportion of the patients show a tendency to confabulate. These effects are found in the absence of any significant deterioration in their performance on tests of reasoning, speed and other, non-frontal focal cognitive tests. The apparently transient impairment on memory tasks and tests of frontal lobe dysfunction is interpreted as reflecting a dysfunction of regions of the frontal lobes affected by oedema, rather than as being due to irrevocable destruction of areas of the brain targeted in the operation. Whether the irrevocably damaged parts of the frontal lobes give rise to long-term subtle deficits which could not be detected by the tests employed in this study remains a possibility and future research may provide further clarification. The fact that the oedema is transient with a corresponding variation in the degree of dysfunction of areas of the frontal lobes suggests that patients undergoing SST are very likely to present with different degrees of neuropsychological deficits at different stages of their post-operative recovery. Repeated neuropsychological studies during the post-operative period in conjunction with other investigations, such as repeated MRI and blood-flow studies, are likely to provide a fertile area of research for the advancement of our understanding of frontal lobe functions.

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REFERENCES

Bartlett JR, Bridges PK (1977) The extended subcaudate tractotomy lesion. In: *Neurosurgical Treatment in Psychiatry, Pain, and Epilepsy.* Edited by W. H. Sweet, S. Obrador and J. G. Martin-Rodriguez. Baltimore and London: University Park Press, pp. 387–398.

Benton AL (1968) Differential behavioral effects in frontal lobe disease. *Neuropsychologia,* **6,** 53–60.

Borkowski JG, Benton AL, Spreen O (1967) Word fluency and brain damage. *Neuropsychologia,* **5,** 135–140.

Bridges PK (1973) Psychosurgery today: psychiatric aspects. *Proceedings of the Royal Society of Medicine,* **65,** 1104–1108.

Corsellis Jan, Jack AB (1973) Neuropathological observations on yttrium implants and on undercutting in the orbito-frontal areas of the brain. In: *Surgical Approaches in Psychiatry.* Edited by L. V. Laitinen and K. E. Livingston. Lancaster: MTP Press, pp. 90–95.

Coughlan AK, Warrington EK (1978) Word-comprehension and word-retrieval in patients with localized cerebral lesions. *Brain,* **101,** 163–185.

Coughlan AK, Hollows SE (1984) Use of memory tests in differentiating organic disorder from depression. *British Journal of Psychiatry,* **145,** 146–167.

Crockett D, Bilsker D, Hurwitz T, Kozak J (1986) Clinical utility of three measures of frontal lobe dysfunction in neuropsychiatric samples. *International Journal of Neuroscience,* **30,** 241–248.

Damasio AR (1985) The frontal lobes. In: *Clinical Neuropsychology.* Second edition. Edited by K. M. Heilman and E. Valenstein. New York and Oxford: Oxford University Press, pp. 339–375.

Delbecq-Derouesné J, Beauvois MF, Shallice T (1990) Preserved recall versus impaired recognition: a case study. *Brain,* **113,** 1045–1074.

De Renzi E, Vignolo LA (1962) The Token Test: a sensitive test to detect receptive disturbances in aphasics. *Brain,* **85,** 665–678.

Flor-Henry P (1969) Psychosis and temporal lobe epilepsy: a controlled investigation. *Epilepsia,* **10,** 363–395.

Flor-Henry P (1984) Hemispheric laterality and disorders of affect. In: *Neurobiology and Mood Disorders*. Edited by R. M. Post and J. C. Ballenger. Baltimore and London: Williams and Wilkins, pp. 467–480.

Göktepe EO, Young LB, Bridges PK (1975) A further review of the results of stereotactic subcaudate tractotomy. *British Journal of Psychiatry*, **126**, 270–280.

Hirst W, Johnson MK, Kim JK, Phelps EA, Risse G, Volpe BT (1986) Recognition and recall in amnesics. *Journal of Experimental Psychology: Learning, Memory and Cognition*, **12**, 445–451.

Jackson M, Warrington EK (1986) Arithmetic skills in patients with unilateral cerebral lesions. *Cortex*, **22**, 611–620.

Joschko M (1986) Clinical and neuropsychological outcome following psychosurgery. In: *Neuropsychological assessment of Neuropsychiatric Disorders*. Edited by I. Grant and K. M. Adams. New York and Oxford: Oxford University Press, pp. 300–320.

Kimura D (1977) Acquisition of a motor skill after left-hemisphere damage, *Brain*, **100**, 527–542.

Knight K (1965) Stereotactic tractotomy in the surgical treatment of mental illness. *Journal of Neurology, Neurosurgery, and Psychiatry*, **28**, 304–310.

Kolb B, Wishaw IQ (1990) *Fundamentals of Human Neuropsychology*. Third edition. New York: W. H. Freeman.

Kopelman MD (1987) Two types of confabulation. *Journal of Neurology, Neurosurgery, and Psychiatry*, **50**, 1482–1487.

Lezak MD (1976) *Neuropsychological Assessment*. New York: Oxford University Press.

Luria AR (1966) *Human Brain and Psychological Processes*. New York: Harper and Row.

McKenna P, Warrington EK (1983) *The Graded Naming Test*. Windsor: NFER-Nelson.

Mercer B, Wapner W, Gardner H, Benson F (1977) A study of confabulation. *Archives of Neurology, Chicago*, **34**, 429–433.

Miller E (1984) Verbal fluency as a function of a measure of verbal intelligence and in relation to different types of cerebral pathology. *British Journal of Clinical Psychology*, **23**, 53–57.

Milner B (1963) Effects of different brain lesions on card sorting: the role of the frontal lobes. *Archives of Neurology, Chicago*, **9**, 90–100.

Milner B (1964) Some effects of frontal lobectomy in man. In: *The Frontal Granular Cortex and Behavior*. Edited by J. M. Warren and K. Akert. New York and London: McGraw-Hill, pp. 313–334.

Milner B (1966) Amnesia following operation on the temporal lobes. In: *Amnesia*. Edited by C. W. M. Whitty and O. L. Zangwill. London: Butterworth, pp. 109–133.

Nelson HE (1976) A modified card sorting test sensitive to frontal lobe defects. *Cortex*, **12**, 313–324.

Nelson HE (1982) *National Adult Reading Test*. Windsor: NFER-Nelson.

Newcombe R (1975) The lesion in stereotactic subcaudate tractotomy. *British Journal of Psychiatry*, **126**, 478–481.

Nie HN, Hull CH, Jenkins JG, Steinbrenner K, Bent DH (1975) *SPSS, Statistical Package for the Social Sciences*. Second Edition. New York: McGraw-Hill.

O'Callaghan MAJ, Carroll D (1982) *Psychosurgery: A Scientific Analysis*. Lancaster: MTP Press.

Perani D, Kartsounis LD, Costello A (1991) Korsakoff's psychosis: a neuropsychological and positron emission tomography study of two cases. In: *Neuropsychology of the Subcortical Structures*. Edited by G. Vallar, S. F. Cappa and C. W. Wallesh. Oxford University Press. In press.

Poynton A, Bridges PK, Bartlett JR (1988) Psychosurgery in Britain now. *British Journal of Neurosurgery*, **2**, 297–306.

Raven JC (1958) *Advanced Progressive Matrices*, Set 1. London: H. K. Lewis.

Shallice T (1982) Specific impairments of planning. *Philosophical Transactions of the Royal Society of London, B*, **298**, 199–209.

Shallice T (1988) *From Neuropsychology to Mental Structure*. Cambridge: Cambridge University Press.

Shallice T, Evans ME (1978) The involvement of the frontal lobes in cognitive estimation. *Cortex*, **14**, 294–303.

Spitzer RL, Endicott J, Robins E (1978) *Research Diagnostic Criteria for a Selected Group of Functional Disorder*. Third edition. New York: Biometrics Research, New York State Psychiatric Institute.

Stuss DT, Benson DF (1986) *The Frontal Lobes*. New York: Raven Press.

Valenstein ES (1980) Historical perspective. In: *The Psychosurgery Debate: Scientific, Legal, and Ethical Perspectives*. Edited by E. S. Valenstein. San Francisco: W. H. Freeman, pp. 11–54.

Warrington EK (1984) *Recognition Memory Test*. Windsor: NFER-Nelson.

WARRINGTON EK, JAMES M (1988) Visual apperceptive agnosia: a clinico-anatomical study of three cases. *Cortex*, **24**, 13–32.
WECHSLER D (1945) A standardized memory scale for clinical use. *Journal of Psychology*, **19**, 87–95.
WECHSLER D (1955) Wechsler Adult Intelligence Scale. New York: The Psychological Corporation.
WILLISON JR (1988) *Neuropsychological Investigations of a Set of Mental Speed Tests*. PhD thesis, University of London.

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IRISH (DONEGAL) AMYLOIDOSIS IS ASSOCIATED WITH THE TRANSTHYRETIN$^{\mathrm{ALA}\ 60}$ (APPALACHIAN) VARIANT

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SUMMARY

A cluster of cases of late onset amyloidosis, presenting chiefly with peripheral neuropathy and cardiac failure, has been described in Donegal, north-west Ireland. Molecular genetic and protein analyses show that two new patients from the same region have a mutation in the transthyretin gene previously reported in a family with an Irish ancestor from the Appalachian region of the United States.

INTRODUCTION

The familial amyloid polyneuropathies (FAP) are a heterogeneous group of autosomal dominant disorders with overlapping phenotypes, which are often labelled according to the place of origin of affected families. The amyloid fibril protein which is deposited in the tissues of patients with most FAPs is a variant form of transthyretin (TTR; formerly known as prealbumin). In the commonest Portuguese type of FAP, the variant TTR has a substitution of methionine for valine at position 30 (Saraiva *et al.*, 1984); this results from a single base change which leads to a new recognition site for the restriction endonuclease *Nsi*I which can be demonstrated by a cDNA probe for the TTR gene (Ide *et al.*, 1986; Holt *et al.*, 1989). Gene carriers for the majority of other types of TTR-related FAP can also be detected by protein or genetic studies (Benson, 1991).

One of us (H.S.) previously reported seven cases of late onset amyloid neuropathy from Donegal in north-west Ireland in this journal (Staunton *et al.*, 1987). The genetic nature of this disorder was suggested by the fact that some patients had similarly affected relatives, the close geographical clustering of the cases, and the presence of TTR-containing amyloid in affected tissues. It was proposed that these patients had the Portuguese type of FAP, as late onset of this disorder is well described, particularly in Swedish patients (Sequeiros and Saraiva, 1987). We now present the results of molecular genetic studies in two further cases of FAP from Donegal, complemented by protein analysis in one. These demonstrate that Donegal amyloidosis is associated with the TTR$^{\mathrm{ala}\ 60}$ variant, previously reported in a family from the Appalachian region of the United States (Benson *et al.*, 1987) and, more recently, a kindred from upstate

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New York (Koeppen *et al.*, 1985, 1990). The point mutation which leads to the substitution of alanine for threonine at position 60 of the TTR molecule can be detected by the restriction endonuclease *Pvu*II (Wallace *et al.*, 1986).

CASE REPORTS

Case 1

This 65-yr-old man originated from Gwedore, Donegal, but lived in London from the age of 12. He first presented in May 1988 with a 9 mth history of alternating constipation and diarrhoea, weight loss of 5 kg, and postural dizziness with near syncope for the previous 2 mths. He had had a few syncopal episodes on standing up 2 yrs previously. Sigmoidoscopy and barium enema were normal. A barium meal and follow through examination showed duodenal scars and endoscopy showed gastritis. A jejunal biopsy was normal. In December 1988 he was referred to the neurology clinic with a 6 wk history of paraesthesiae and numbness in the hands and numbness in the legs.

The patient has 3 sons and 2 daughters aged between 27 and 36 yrs who were all normal on neurological examination. His father died suddenly aged 70 yrs, and his walking had been impaired in later years. His mother died at the age of 77 yrs, with no known neurological disease. The patient had nine siblings, two of whom died suddenly aged 41 and 51, one with chest pain, and three others are thought to have ischaemic heart disease. He is not known to be related to the previously described patients (Staunton *et al.*, 1987).

On examination his blood pressure was 130/80 lying and 100/60 standing, with a pulse rate of 60. He had wasting and weakness of the small hand muscles. All tendon reflexes were present but the ankle jerks were depressed. There was impairment of all sensory modalities in the hands and in a stocking distribution up to the knees.

Nerve conduction studies showed slight reduction of motor nerve conduction velocities in the right median (44 m/s), ulnar (47 m/s) and common peroneal (37 m/s) nerves, with distally evoked muscle action potential amplitudes of 6.6 and 1.9 mV from abductor digiti minimi and extensor digitorum brevis. The right radial, median and ulnar sensory action potentials (SAPs) were not detectable, and the amplitude of the left ulnar and right sural nerve SAPs were 1 and 0.5 μv, respectively. A full thickness sural nerve biopsy showed no inflammatory cells and no amyloid material was seen in serial sections on light or electron microscopy. There was striking loss of myelinated fibres, density 1049/mm^2 (normal >6000/mm^2; Jacobs and Love, 1985), with a total fibre count of 1289. A few regenerating clusters were seen There was evidence of active degeneration in teased fibre preparations. Morphometry of myelinated fibres showed a normal bimodal distribution with no preferential loss of small fibres.

An ECG showed first degree heart block. R-R interval variation with posture, tilt test and the Valsalva manoeuvre were abnormal. An echocardiogram showed thickening of the wall of the left ventricle with reduction of intraventricular size; the appearances were consistent with cardiac amyloidosis. A rectal biopsy showed vascular and extracellular deposits of amorphous material in the submucosa which stained with congo red and methyl violet and showed green birefringence under polarized light. Serum transthyretin was 190 μg/l (normal 170−420 μg/l). Investigations for malabsorption showed increased faecal fat at 28 mmol/day (normal 0−18) with abnormal xylose absorption at 2 and 5 h and a normal pancreolauryl test.

His condition gradually deteriorated. He continued having intermittent diarrhoea in spite of courses of antibiotics and codeine phosphate. His postural hypotension was partly controlled with fludrocortisone. Painful paraesthesiae in the limbs responded to carbamazepine. By mid-1990 he had become wheelchair bound and had severe wasting and weakness in upper and lower limbs, more marked distally, absent tendon reflexes and sensory impairment to above the elbows and mid-thighs. He had a further episode of loss of consciousness followed by a seizure in May 1990. In August 1990 a 24 h ECG tape showed intermittent first, second and third degree heart block, with periods of asystole lasting up to 8 s; a cardiac pacemaker was inserted.

Case 2

This 67-yr-old female was the sister of Case 6 in the previous report and originated from Gortnatraw, Donegal (*see* Fig. 1, Staunton *et al.*, 1987). She first presented with angina in 1977 and was subsequently treated with beta blockers for chest pain and intermittent hypertension. In 1981 electrocardiography (ECG) showed mild generalized T wave flattening and subsequently demonstrated first degree atrioventricular block or atrial fibrillation. Beta blockade was stopped in 1989 because of postural hypotension.

She was admitted to hospital in January 1990 complaining of weight loss and pain in all limbs, particularly burning sensations in the legs. She had not walked unaided for 1 yr and had been confined to bed for 1 mth She was in atrial fibrillation with a normal ventricular rate. There was diffuse muscle wasting and weakness in all four limbs. The tendon reflexes were absent. Sensation was normal in the arms, but pain appreciation was reduced to mid-thigh, and touch to mid-calf. Vibration and position sense was impaired distally in the legs. No nerve conduction or detailed autonomic function data are available. A sural nerve biopsy showed two foci of interstitial congophilic material demonstrating apple green birefringence. The patient died in March 1990; no autopsy was performed.

METHODS

Genomic DNA was extracted from 10 ml of blood from both subjects using standard methods (Old, 1986). This was digested with the restriction endonucleases *Nsi*I and *Pvu*II under conditions recommended by the manufacturers (New England Biolabs and Northumbria Biologicals Ltd.). Fragments of DNA were electrophoresed in 0.8% agarose gels overnight and then transferred to nylon filters (Genescreen Plus, New England Nuclear) by means of Southern blotting. A 500 base pair portion of a human TTR cDNA probe (cloned in plasmid SP65) was labelled with ^{32}P (Feinberg and Vogelstein, 1983) and then hybridized to the filters prior to autoradiography at −70°C for 2−5 days.

TTR was isolated from 1 ml of serum of Case 1 by Affi-Gel Blue affinity chromatography (BioRad Laboratories), anti-human TTR IgG Affi-Gel 10 immunoaffinity chromatography, and finally purified by reverse phase high performance liquid chromatography (HPLC) on a TSK phenyl 5PW RP column (Toso Co. Ltd.). The purified TTR was digested with trypsin and the products analysed by reverse phase HPLC on a TSK ODS SIL 120A column prior to automated sequence analysis (Applied Biosystems 470A) of two peptides corresponding to TTR amino acids 49−70 and 49−76 (Nakazato *et al.*, 1984).

RESULTS

On DNA analysis, the Portuguese FAP mutation (leading to a *Nsi*I site gain) was not detected, but both patients had the mutation underlying the TTR$^{\text{ala}\,60}$ variant,

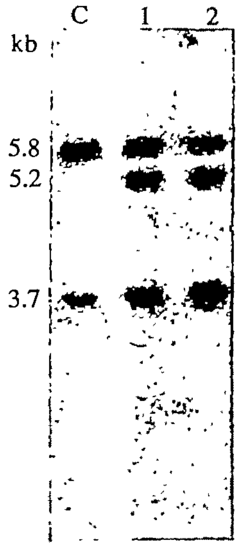

FIG. 1 Transthyretin gene analysis in a control subject (C, *left lane*) and Cases 1 and 2 (*middle* and *right lanes*) The patients have a 5.2 kb DNA fragment in addition to the normal 5.8 and 3.7 kb bands after digestion of genomic DNA with *Pvu*II and hybridization to a cDNA TTR probe. The TTR$^{\text{ala}\,60}$ mutation produces a restriction site for *Pvu*II (normal sequence in this region 5′ CAACTG 3′, mutant 5′ CAGCTG 3′ which is restriction site), hence cutting one of the two homologous 5.8 kb fragments into two of 5.2 and 0.6 kb (latter not shown).

demonstrated by a restriction site gain for *Pvu*II (Fig. 1). This was confirmed by peptide sequencing in Case 1, with a substitution of alanine for threonine at position 60 of the TTR molecule. The ratio of normal to variant TTR was approximately 3:2.

DISCUSSION

The clinical features of the two patients described here are similar to those reported previously in Donegal and the United States, with late onset of a multisystem disease in which symptoms and signs of peripheral neuropathy may be overshadowed at the time of presentation by postural syncope, cardiac conduction defects, or diarrhoea (Koeppen *et al.*, 1985; Benson *et al.*, 1987; Staunton *et al.*, 1987). The late onset of this disorder, together with the likely probability that the neuropathy and the possibility of amyloidosis are overlooked in some affected individuals, explains the seemingly sporadic nature of several patients with this dominantly inherited disorder. It is possible that some gene carriers never develop the disease, even in advanced age, as occurs in the Portuguese type of FAP (Nakazato *et al.*, 1987; Sequeiros and Saraiva, 1987; Holt *et al.*, 1989).

Some types of FAP have characteristic presentations (Thomas and Harding, 1990; Benson, 1991). The degree of muscle weakness and wasting, early upper limb involvement, and prominent loss of vibration and position sense are particularly striking in our patients and others with the $\mathrm{TTR}^{\mathrm{ala}\ 60}$ variant (Koeppen *et al.*, 1985; Benson *et al.*, 1987; Staunton *et al.*, 1987), as compared with most other types of FAP which typically present with distal loss of pain and temperature appreciation in the legs. However, distinction between these disorders is often impossible in individual cases, and FAP may sometimes be confused with acquired causes of amyloidosis. There is also an intrinsic difficulty of pathological diagnosis as amyloid deposits are patchy in FAP (Thomas and Harding, 1990). This is illustrated by Case 1, in whom amyloid was detectable in rectal tissue but not in nerve. This problem is less clinically important now that TTR gene analysis provides a rapid and non-invasive means of diagnosing the different known types of TTR-related FAP, including in apparently sporadic cases. Accurate diagnosis has important implications for genetic counselling.

Our observations have delineated a second geographical cluster of $\mathrm{TTR}^{\mathrm{ala}\ 60}$ FAP. It is probable that the Donegal cases and the families reported in the United States share a common ancestor. The ancestral couple from which the Appalachian family was descended settled in western Virginia in the early 1800s; the husband originated from Ireland (Benson *et al.*, 1987). The kindred described by Koeppen *et al.* (1985, 1990) is also of Irish descent (A. H. Koeppen, personal communication). Irish/Appalachian amyloidosis appears to be a more appropriate geographical label for this disease.

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REFERENCES

BENSON MD (1991) Inherited amyloidosis. *Journal of Medical Genetics*, **28**, 73–78.

BENSON MD, WALLACE MR, TEJADA E, BAUMANN H, PAGE B (1987) Hereditary amyloidosis: description of a new American kindred with late onset cardiomyopathy: Appalachian amyloid. *Arthritis and Rheumatism*, **30**, 195–200

FEINBERG AP, VOGELSTEIN B (1983) A technique for radiolabeling DNA restriction endonuclease fragments to high specific activity. *Analytical Biochemistry*, **132**, 6–13.

HOLT IJ, HARDING AE, MIDDLETON L, CHRYSOSTOMOU G, SAID G, KING RHM *et al.* (1989) Molecular genetics of amyloid neuropathy in Europe. *Lancet*, **i**, 524–526.

IDE M, MITA S, IKEGAWA S, MAEDA S, SHIMADA K, ARAKI S (1986) Identification of carriers of mutant prealbumin gene associated with familial amyloidotic polyneuropathy type I by Southern blot procedures: study of six pedigrees in the Arao district of Japan. *Human Genetics*, **73**, 281–285.

JACOBS JM, LOVE S (1985) Qualitative and quantitative morphology of human sural nerve at different ages. *Brain*, **108**, 897–924.

KOEPPEN AH, MITZEN EJ, HANS MB, PENG S-K, BAILEY RO (1985) Familial amyloid polyneuropathy. *Muscle and Nerve*, **8**, 733–749.

KOEPPEN AH, WALLACE MR, BENSON MD, ALTLAND K (1990) Familial amyloid polyneuropathy: alanine-for-threonine substitution in the transthyretin (prealbumin) molecule. *Muscle and Nerve*, **13**, 1065–1075.

NAKAZATO M, KANGAWA K, MINAMINO N, TAWARA S, MATSUO H, ARAKI S (1984) Identification of a prealbumin variant in the serum of a Japanese patient with familial amyloidotic polyneuropathy. *Biochemical and Biophysical Research Communications*, **122**, 712–718.

NAKAZATO M, TANAKA M, YAMAMURA Y, KURIHARA T, MATSUKURA S, KANGAWA K *et al.* (1987) Abnormal transthyretin in asymptomatic relatives in familial amyloidotic polyneuropathy. *Archives of Neurology, Chicago*, **44**, 1275–1278.

OLD JM (1986) Fetal DNA analysis. In: *Human Genetic Diseases: A Practical Approach.* Edited by K. E. Davies. Oxford: IRL Press, pp. 1–17.

SARAIVA MJM, BIRKEN S, COSTA PP, GOODMAN DS (1984) Amyloid fibril protein in familial amyloidotic polyneuropathy, Portuguese type. *Journal of Clinical Investigation*, **74**, 104–119.

SEQUEIROS J, SARAIVA MJM (1987) Onset in the seventh decade and lack of symptoms in heterozygotes for the $\mathrm{TTR}^{\mathrm{Met30}}$ mutation in hereditary amyloid neuropathy—type I (Portuguese, Andrade). *American Journal of Medical Genetics*, 27, 345–357.

STAUNTON H, DERVAN P, KALE R, LINKE RP, KELLY P (1987) Hereditary amyloid polyneuropathy in North West Ireland. *Brain*, **110**, 1231–1245.

THOMAS PK, HARDING AE (1990) Peripheral neuropathies. In: *Principles and Practice of Medical Genetics*, Volume I. Edited by A. E. H. Emery and D. L. Rimoin. Edinburgh: Churchill Livingstone, p. 421.

WALLACE MR, DWULET FE, CONNEALLY PM, BENSON MD (1986) Biochemical and molecular genetic characterization of a new variant prealbumin associated with hereditary amyloidosis. *Journal of Clinical Investigation*, **78**, 6–12.

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PLATEAU-WAVE PHENOMENON (I)

CORRELATION BETWEEN THE APPEARANCE OF PLATEAU WAVES AND CSF CIRCULATION IN PATIENTS WITH INTRACRANIAL HYPERTENSION

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SUMMARY

Plateau waves, as described by Lundberg (1960), can often be observed in patients with increased intracranial pressure (ICP) resulting from brain tumours, benign intracranial hypertension and other causes. The clinical significance of the waves, however, is still debated. In this study, the ICP was recorded continuously, the size of the ventricular system was evaluated using computerized tomography (CT), the cerebrospinal fluid (CSF) flow was studied using isotope cisternography, and the absorptive capacity of the CSF was determined by measuring the conductance to CSF outflow, in 94 patients with increased ICP. All patients who received continuous ICP monitorings had a basic ICP level of more than 200 mmHg, and these patients were assigned to two groups on the basis of the presence or absence of the plateau waves in the ICP recordings: group I comprising 17 patients without plateau waves but with a high ICP resulting from subarachnoid haemorrhage or hypertensive intracerebral haemorrhage, within 5 days after the start of bleeding; and group II consisting of 77 patients with both plateau waves and a high ICP resulting from brain tumours, meningitis carcinomatosa, benign intracranial hypertension, superior sagittal sinus thrombosis and communicating hydrocephalus. The isotope cisternography and conductance to CSF outflow studies showed that there was neither a delay in CSF circulation nor an impairment of CSF absorption in the group 1 patients and these patients showed no ventricular dilatation on CT, whereas there was a marked sluggishness in the CSF flow and a severe defect in the CSF absorption capacities of the group II patients irrespective of the presence or absence of ventricular dilatation on CT. The present observations indicate that patients with a plateau-wave phenomenon have a marked impairment of CSF absorption and CSF flow. We suggest that the phenomenon is an important sign indicating an impairment of CSF absorption capacities.

INTRODUCTION

Plateau waves, as described by Lundberg (1960), can often be observed in patients with increased intracranial pressure (ICP) resulting from brain tumours, benign intracranial hypertension, hydrocephalus, and other causes. Typical plateau waves are characterized by rapid increase and decrease of ICP to and from an ICP level of considerable height and varying duration (usual ranges: 50–100 mmHg, 5–20 min) and often irregular occurrence without premonitory symptoms or obvious precipitating factors (Lundberg, 1960). The origin and clinical significance of plateau waves, however, are still debated and are of considerable interest to neurologists and neurosurgeons.

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In our department the preoperative and/or postoperative ICP has been monitored continuously in patients with increased ICP (with a basic ICP level of more than 20 mmHg) resulting from space-occupying lesions, intracranial haemorrhages, and other causes, as a guide to appropriate therapy for the increased ICP. In this study, we have analysed patients whose ICP recordings were carried out for 12 h or more, evaluated ventricular system size by computed tomography (CT), cerebrospinal fluid (CSF) flow by studying isotope cisternography and resistance to CSF absorption by examining conductance to CSF outflow. By these means, we have attempted to clarify whether there is a relationship between the development of the plateau waves and the level of ICP, the fluctuation pattern of ICP, the flow of CSF, and the resistance to the absorption of CSF.

SUBJECTS AND METHODS

Patients

For this study, we examined 94 patients with increased ICP. Forty-eight were males and 46 were females. Their ages ranged from 21 to 76 yrs, with a mean age of 53 yrs. Several kinds of intracranial lesions with increased ICP were represented, and the diagnoses and number of patients are given in Table 1. Cases with infratentorial mass lesions, acute hydrocephalus following subarachnoid haemorrhage (SAH) and normal pressure hydrocephalus were omitted from this study. Written informed consent was obtained from each patient and/or family prior to the study.

ICP recordings

The ICP was recorded from an indwelling ventricular catheter placed in the frontal horn of the lateral ventricle, preferably on the right side, and connected to a pressure transducer. This method was based on that described by Lundberg (1960). The ICP was continuously monitored on two paper-chart polyrecorders for a period ranging from 12 to 37 (mean 29) h. We used paper-chart speeds of 2 cm/min in one polyrecorder for detailed analysis of the pressure curve, and of 12 cm/h in the other for an overview of the entire ICP course.

There were 5 patients who developed complications attributable to the indwelling ventricular catheter: 2 with intracerebral haematomas (both brain-tumour patients) and 3 with infection (1 of these with SAH, 1 with hypertensive intracerebral haemorrhage, and 1 with a brain tumour). All of them were controlled by conservative methods. Increased ICP was usually treated by hyperventilation and/or osmotic agents, such as mannitol or glycerol, and if these treatments were ineffective in reducing high ICP, continuous ventricular drainage was carried out.

The mean ICP was calculated as the diastolic pressure plus one-third of the pulse pressure. Pressure waves, that is, the ICP irregularities, were defined according to Lundberg's description (1960). Rhythmic waves in the ICP were identified as oscillations with a frequency of 2.5 per min (B-waves), closely related to the respiration, and with a frequency of 4–8 per min (C-waves), closely related to variations of the systemic arterial blood pressure. Plateau waves recurred at intervals of varying length. The frequency of the rhythmic waves was expressed as a percentage of the total hours of study, and was calculated by dividing the number of hours in which rhythmic waves occurred by the total hours of study. The frequency of the plateau waves was expressed in the same way as that of the rhythmic waves. In this study a high ICP was defined as one having a resting pressure of more than 20 mmHg for 50% or more of the ICP monitoring period.

CT scanning

CT scanning was performed so as to evaluate the sizes of the brain lesions and of the ventricular system. The ventriculocranial ratio obtained by the method of Vassilouthis and Richardson (1979) (the ratio of the width of the lateral ventricle at the level of the foramen of Monro to that of the transverse inner diameter of the skull at the same level) was used to evaluate ventricular dilatation. This ratio is less than 0.15 in normal subjects (Vassilouthis and Richardson, 1979). In this study, patients diagnosed as having hydrocephalus had ventriculocranial ratios of between 0.22 and 0.31.

Isotope cisternography

Isotope cisternography was carried out using a lumbar injection of 1 mCi of indium-111-DTPA (diethylenetriaminepenta-acetic acid). Sequential lateral and posterior scintiscans of the head were obtained with a scintillation camera at approximately 2, 6, 24 and 48 h after the injection. The intracranial isotope activity at each interval was calculated (with correction for environmental background effects and decay) as a percentage of the maximum value. Clearance of CSF was defined by the occurrence of peak isotope activity and by the levels of the residual activity at 2, 6, 24 and 48 h. In normal clearance, maximum intracranial activity as revealed by isotope cisternography is reached at 6 h, followed by a gradual decrease to levels of between 40% and 80% of peak activity at 24 h and between 25% and 40% at 48 h; the peak activity is not reached until 24 and 48 h in delayed clearance (Curl *et al.*, 1972). Cisternography was carried out just prior to or just after the continuous ICP monitoring.

Conductance to CSF outflow

The conductance to CSF outflow was measured by the lumbo-ventricular perfusion method of Børgesen *et al.* (1978). Following ICP monitoring, physiological saline solution was infused through a lumbar cannula at rates (V_{in}) varying between 0.5 and 4.0 ml/min. The ICP level was controlled by the height of the outflow orifice of the catheter from the ventricle. The volume of the outflow (V_{out}) from the outflow tube connected to the ventricular catheter, was measured gravimetrically in 2 periods of 5 min at 3 to 5 different ICP levels, obtained by elevating the outflow orifice of the catheter. In this study, we chose to estimate the CSF formation rate (V_{CSF}) to be 0.37 ml/min, because the estimated CSF formation rate reported was 0.35–0.37 ml/min, obtained using ventriculo-cisternal perfusion techniques (Rubin *et al.*, 1966; Cutler *et al.*, 1968), and 0.36–0.39 ml/min in the group I and group II patients in this study (Table 2) when the CSF volume drained and the time required for the pressure return were determined (Masserman, 1934; Johnston and Paterson, 1974). The CSF volume absorbed per min (V_{abs}) was then calculated from the following formula: $V_{abs} = V_{in}+V_{CSF}-V_{out}$ (Børgesen *et al.*, 1978). The V_{abs} was plotted against the different ICP values and the slope of the resulting regression line expressed the conductance to CSF outflow (Børgesen *et al.*, 1978). It has been reported that patients with normal CSF absorption capacity have a conductance to CSF outflow of more than 0.12 ml/min (Børgesen *et al.*, 1978, 1979; Ekstedt, 1978; Sklar *et al.*, 1979; Gjerris *et al.*, 1982, 1985; Hansen *et al.*, 1987).

Study protocol

The study protocol is shown in Table 1. The patients were divided into two groups on the basis of their ICP monitoring patterns as described here. Group I comprised 17 patients without plateau waves but with a high ICP in their continuous ICP recordings within 5 d after the start of bleeding: 7 with SAH due to rupture of an intracranial aneurysm (3 preoperative and 4 postoperative) and 10 with hypertensive intracerebral haemorrhage (7 thalamic and 3 putaminal haemorrhages). The ruptured intracranial aneurysms were associated with the anterior communicating artery in 3 cases, the vertebrobasilar artery in 2, and the internal carotid artery in 5. Our policy with regard to the management of ruptured intracranial aneurysm is as follows; in patients in good physical condition [grades I to III of Hunt and Hess (1968)] the aneurysm is repaired within 48 h of the start of bleeding. Patients whose condition is poor [grades IV and V of Hunt and Hess (1968)] are treated only with ventricular drainage to control increased ICP until they improve. Those who have massive intracerebral haematomas are operated on at once, irrespective of their condition, to evacuate the haematoma prior to the repair of aneurysm. In group II there were 77 patients with plateau waves and with a high ICP: 34 with supratentorial intracranial tumours (11 glioblastoma multiforme, 7 astrocytomas and 16 metastatic brain tumours), 4 with meningitis carcinomatosa, 8 with benign intracranial hypertension, 3 with superior sagittal sinus thrombosis and 28 with communicating hydrocephalus after SAH (more than 10 d after the start of bleeding) (Table 1). In each group, ICP monitoring, CT, isotope cisternography, measurements of estimated rate of CSF formation and conductance to CSF outflow were studied (Table 1).

Lumbar CSF pressure recordings

Lumbar CSF pressure monitoring was carried out through a lumbar subarachnoid catheter simultaneously with the ventricular ICP monitoring in order to estimate the rate of CSF formation (15 patients) and to measure the conductance to CSF outflow (33 patients) (Tables 1, 2 and 3). The patients who received the estimated CSF formation rate had a mean basic ICP level of between 22 and 29 mmHg. Group I comprised

TABLE 1. DIAGNOSES, NUMBER OF PATIENTS AND PROTOCOL FOR STUDYING ICP MONITORING, CT, CISTERNOGRAPHY, CSF FORMATION RATE ESTIMATION AND CONDUCTANCE TO CSF OUTFLOW MEASUREMENT

			Protocol				
Group	*Diagnosis*	*No. of patients*	*ICP*	*CT**	*Cisternography*	*CSF formation rate*	*Conductance to CSF outflow*
I	SAH (within 5 d after bleeding)	7	7	7(0)	5	3	5
	HICH (within 5 d after bleeding)	10	10	10(0)	5	2	5
II	Brain tumour	34	34	34(0)	7	2	6
	Meningitis carcinomatosa	4	4	4(4)	0	1	3
	BIH	8	8	8(0)	8	4	4
	SSS thrombosis	3	3	3(0)	4	0	2
	Communicating hydrocephalus (more than 10 d after SAH)	28	28	28(28)	17	3	8
	Total	94	94	94(32)	46	15	33

ICP = intracranial pressure monitoring. CT = computerized tomography, CSF = cerebrospinal fluid, SAH = subarachnoid haemorrhage; HICH = hypertensive intracerebral haemorrhage; BIH = benign intracranial hypertension; SSS = superior sagittal sinus *Numbers in parentheses in the column of CT indicate the numbers of patients with hydrocephalus

5 patients: 3 with SAH (postoperative cases) and 2 with preoperative hypertensive intracerebral haemorrhage (putaminal haemorrhage cases) with haematoma volumes of 21 and 26 ml on CT, respectively. In group II, there were 10 patients: 2 with preoperative brain tumours (astrocytomas), both in the left frontal lobe with a tumour-size diameter of 2.5 cm and 2.8 cm on CT, respectively, 1 with meningitis carcinomatosa and 3 with communicating hydrocephalus with the symmetrical enlarged lateral and the III ventricles on CT and 4 with benign intracranial hypertension with the symmetrical normal sized ventricles on CT. We considered that, in these patients, the procedure of CSF drainage through the lumbar cannula had little or no risk of developing brain herniation.

RESULTS

Mean ICP level and ICP pattern

Mean ICP levels in the individual patients in group I ranged from 26 to 58 mmHg. The frequency of rhythmic waves (B- and C-waves) in this group was between 68% and 92% (mean 78%) and that of plateau waves was 0%. An ICP recording typical of this group, seen in a patient with SAH (3 d after bleeding), is shown in Fig. 1. The mean ICP level in the individual patients in group II ranged from 28 to 87 mmHg, and the frequency of plateau waves was between 18% and 73% (mean 35%), and of rhythmic waves between 34% and 65% (mean 43%). A typical group II patient's ICP recording is shown in Fig. 2.

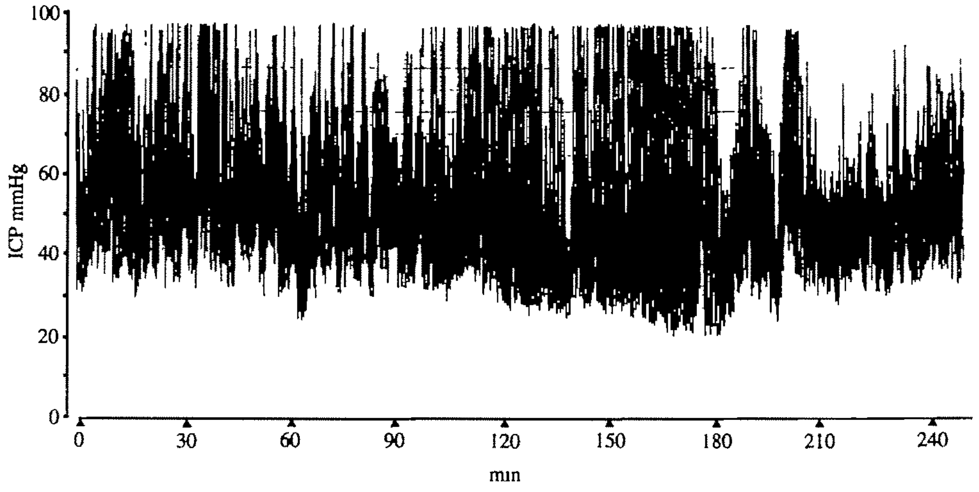

FIG. 1. A 46-yr-old male, subarachnoid haemorrhage due to rupture of left internal carotid artery aneurysm Intracranial pressure (ICP) recording was made 3 d after haemorrhage Typical ICP pattern in group I, showing only frequent rhythmic fluctuations.

CT findings

None of the patients in group I had ventricular dilatation in spite of the high ICP, whereas 32 of the 77 group II patients showed dilated ventricles, and the remaining 45 patients had no hydrocephalus on CT. The ventricular dilatation in the group II patients was a result of meningitis carcinomatosa and communicating hydrocephalus after SAH, and absence of ventricular dilatation was seen in cases of brain tumours, benign intracranial hypertension and superior sagittal sinus thrombosis (Table 1).

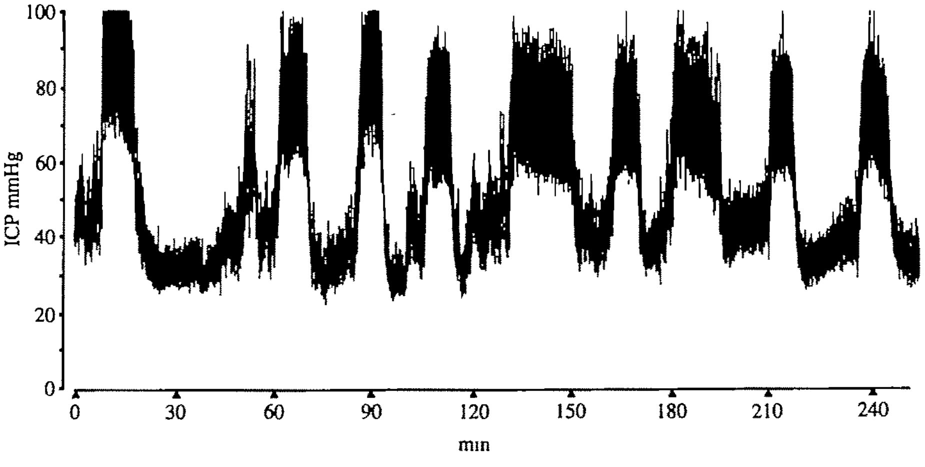

FIG. 2. A 29-yr-old female, glioblastoma multiforme of the right occipital lobe. Recording of intracranial pressure (ICP) showing frequent typical plateau waves at varying intervals. Typical ICP pattern in group II.

Isotope cisternographic findings

The isotope cisternograms in the group I patients showed a normal pattern in 6 cases and a partial block of the subarachnoid space over one cerebral hemisphere in 4. Transient ventricular filling in the early images (2-h or 6-h images, or both) were seen in 3 cases. The cisternograms in the group II patients with ventricular dilatation on CT showed a complete obstruction of the subarachnoid space over both cerebral convexities and revealed the enlarged ventricles in both the 24-h and 48-h images. On the other hand, the cisternograms in the group II patients without ventricular dilatation on CT revealed a large accumulation of radioactivity over the cerebral convexities in the 24-h and 48-h images. In these images, partial blockage of the subarachnoid space was seen in 3 brain tumour patients.

The headcount rates of isotopes in the group I patients showed that the maximum intracranial activity as reached at 6 h in all patients, followed by a gradual decrease to 63% at 24 h, and to 30% at 48 h (Fig. 3), suggesting that there was no sluggishness in the CSF circulation. Those in the group II patients, however, demonstrated that the peak isotope activity was not reached until 24 h (26 patients) or 48 h (9 patients) in any of the patients (with one exception), irrespective of the presence or absence of ventricular dilatation on CT (Fig. 4), and irrespective of the isotope cisternographic pattern, and suggested that there was a marked sluggishness in the CSF circulation in most of the patients in this group. One patient in group II, however, showed maximal intracranial activity at 6 h, followed by a gradual decrease to levels of 80% and 34% of peak activity at 24 h and 48 h, respectively. The diagnosis of this patient was communicating hydrocephalus after SAH; the ventricular dilatation on the CT was mild, and the ventriculocranial ratio was 0.22.

Estimated rate of CSF formation

The CSF formation rate was estimated by dividing the drained CSF volume through a lumbar subarachnoid catheter by the average time required for the CSF pressure to

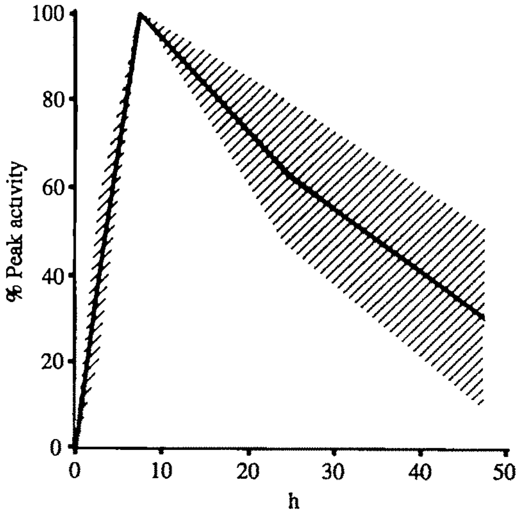

FIG 3. Normalized isotope activity after lumbar intrathecal injection of isotopes in 10 group I patients

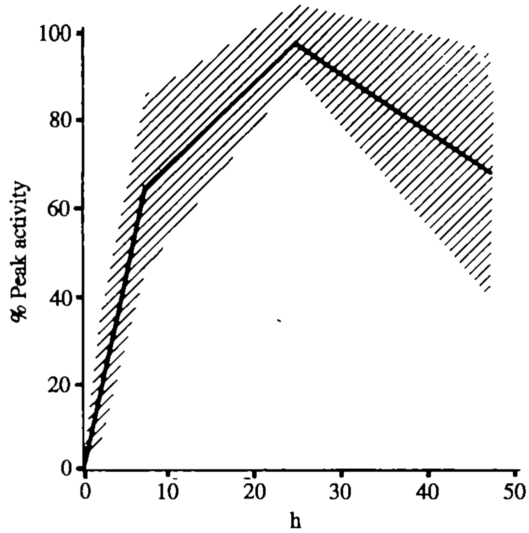

FIG. 4. Normalized isotope activity after lumbar intrathecal injection of isotopes in 36 group II patients.

return to the pre-drainage pressure level, giving values of 0.36 ml/min for group I patients, and 0.39 ml/min for group II patients (Table 2).

Conductance to CSF outflow

The range (minimum and maximum values) and mean values of the conductance to CSF outflow are shown in Table 3. The mean conductance to CSF outflow in the group I patients was normal: 0.143 ml/min/mmHg, suggesting normal CSF absorption capacities; while that in the group II patients was markedly reduced: 0.041 ml/min/mmHg, suggesting the presence of abnormally low CSF absorption capacities.

DISCUSSION

Lundberg (1960) distinguished two main types of spontaneous ICP variations in patients with intracranial hypertension, namely rhythmic waves (B- and C-waves) and plateau waves (A-waves). The origin of the rhythmic waves has been suggested to be related to an intrinsic rhythmic activity of the medullary centres, when this was no longer under the control of the higher centres of the upper brainstem and regarded as a sign of brainstem dysfunction (Lundberg, 1960). That of the plateau waves, on the other hand, is believed to be different, and two major factors have been proposed for their development: a cerebral vasomotor reaction and a taut intracranial condition. Concerning the former factor, it has been shown that the elevation of the ICP at the beginning of the plateau wave is caused by dilatation of the cerebral vessels, while subsequent decline is caused by constriction of these vessels (Lundberg, 1960; Kjällquist *et al.*, 1964; Lundberg *et al.*, 1968, 1974; Risberg *et al.*, 1969), and it is hypothesized that the medullary depressor area may play a role in eliciting this cerebral vasomotor reaction (Hayashi *et al.*, 1987). As to the latter factor, it has been suggested that the intracranial CSF may play an important role in the development of the taut and high-pressure conditions (Hayashi *et al.*, 1982, 1986).

TABLE 2 EFFECTS OF TEMPORARY DRAINAGE OF CSF ON ICP AND ESTIMATED RATE OF CSF FORMATION IN GROUP I AND GROUP II PATIENTS

	Baseline ICP level		*Time to recover (min)*	*CSF volume drained (ml)*	*Estimated CSF formation rate (ml/min)*
	Initial (mmHg)	*Final (mmHg)*			
Group I (n = 5)	36±9	10±3	56±18	20±7	0.36
Group II (n = 10)	27±12	7±4	61±16	24±9	0.39

CSF = cerebrospinal fluid; ICP = intracranial pressure. Values are means±SD

TABLE 3 CONDUCTANCE TO CSF OUTFLOW IN GROUP I AND GROUP II PATIENTS

	Conductance to CSF outflow (ml/min/mmHg)			
	Range			
	Minimum	*Maximum*	*Mean±SD*	*Significance**
Group I (n = 10)	0.112	0.214	0.143±0.026	$P < 0.01$
Group II (n = 23)	0.019	0.093	0.041±0.027	

CSF = cerebrospinal fluid. *Significance was determined by *t* test by comparing the value for group I patients to that for group II patients.

Previously, the role of CSF in the development of plateau waves was tentatively described as follows: the CSF may be squeezed out from the intracranial fluid spaces during either the rising phase or the plateau phase of the waves, and the CSF space may be refilled between the waves before the next wave begins (Lundberg, 1960). This assumption, however, suggests that the intracranial CSF may act as a variable in the development of plateau waves.

Schlesinger *et al.* (1965) studied a patient with increased ICP whose symptoms were severe headache coupled with high grade papilloedema, and they noticed, after isotope instillation into the lumbar sac, an unusual slowing of movement of tagged material along with atypical parasagittal pooling of the material. Absorption from these convexity lakes was slow and several days passed before its final disappearance from the central nervous system. Van Crevel (1979) also reported that impaired CSF absorption at the superior sagittal sinus was the main cause of the raised CSF pressure and papilloedema associated with supratentorial tumours. Johnston and Paterson (1974) reported that in patients with benign intracranial hypertension there was a marked defect in CSF absorption and the reduced CSF absorption was due either to an increase in pressure within the superior sagittal sinus or to an increase in the resistance to CSF flow across the arachnoid villi. Penning and Front (1975), on the other hand, claimed that isotope cisternography in patients with communicating hydrocephalus revealed three principal phenomena: blockage of the CSF pathways, ventricular filling and delayed CSF absorption. In the present study, the cisternographic pattern in the group I patients showed a normal or only partially blocked condition, while the pattern in the group II patients without hydrocephalus on CT showed a large accumulation of radioactivity over the cerebral convexities in the 24-h and 48-h images. That in the group II patients with hydrocephalus showed a complete obstruction of the subarachnoid space over both cerebral convexities and persistent visualization of the enlarged ventricles in the 24-h and 48-h images.

The isotope clearance of the cisternographic study also demonstrated that maximum intracranial isotope activity was reached at 6 h, followed by a gradual decrease at 24-h and 48-h images in the group I patients who had no ventricular dilatation on CT, whereas the peak isotope activity was not, except in one case, reached in 24-h and 48-h images after the isotope injection in the group II patients, irrespective of the presence or absence of hydrocephalus on CT. Thus, the studies of both the cisternographic pattern and isotope clearance indicated that there was no delay in CSF circulation in the group I patients, whereas the group II patients had a markedly sluggish CSF flow.

There are several methods for evaluating the capacity for CSF absorption in humans. One is by measuring conductance to CSF outflow by a constant lumbar pressure infusion test (Ekstedt, 1978; Sklar *et al.*, 1979) and the lumbo-ventricular perfusion test (Børgesen *et al.*, 1978). The conductance has been studied in several intracranial pathologies, such as normal pressure hydrocephalus (Børgesen *et al.*, 1979), benign intracranial hypertension (Sklar *et al.*, 1979; Gjerris *et al.*, 1985), high pressure hydrocephalus (Gjerris *et al.*, 1982) and other causes (Hansen *et al.*, 1987), and it was suggested that conductance values below 0.10–0.12 ml/min/mmHg may have a significant CSF absorptive defect. In this study, the mean value of conductance in the group I patients was normal (0.143 ml/min/mmHg), suggesting no defect in the capacity for CSF absorption, while the mean value in the group II patients was markedly reduced (0.041 ml/min/mmHg), indicating the presence of abnormally low CSF absorption capacities. These observations obtained from the conductance to CSF outflow indicated that the group I patients had no disturbance in CSF absorption capacity in spite of the presence of a high ICP, whereas the group II patients had an abnormally low CSF absorption capacity, irrespective of the presence or absence of hydrocephalus on CT.

Masserman (1934) estimated the rate of CSF formation in patients by measuring the time required for the return of the initial CSF pressure level following removal of a measured amount of CSF by drainage. There were, however, some criticisms that the CSF formation is affected by drainage, and hence the technique of ventricular perfusion was introduced as a precise and physiological method for studying CSF formation (Rubin *et al.*, 1966; Cutler *et al.*, 1968). Katzman and Hussey (1970), however, stated that their results (average formation rates of 0.37 ml/min obtained by Rubin *et al.*, 1966, and of 0.35 ml/min by Cutler *et al.*, 1968) were strikingly similar to the rate of 0.32 ml/min obtained by Masserman (1934). In the present study, the CSF formation rate was estimated by the method suggested by Masserman (1934) and Johnston and Paterson (1974), which yielded values of 0.36 ml/min in group I and 0.39 ml/min in group II, both rates similar to the 0.37 ml/min adult secretion rate reported by Rubin *et al.* (1966), but slightly higher than the 0.30–0.32 ml/min of Masserman (1934), Katzman and Hussey (1970) and Lorenzo *et al.* (1970). Our results obtained from the CSF formation rate may indicate that there is no causal relationship between the ICP increase and the CSF production in the two groups.

The present observations all indicated that the group I patients without plateau waves but with high ICP in their continuous ICP recordings had neither an impairment of CSF absorption capacities nor a delay in CSF circulation, whereas the group II patients with both plateau waves and high ICP in the continuous ICP recordings had a marked sluggishness in the CSF flow and a severe defect in CSF absorption. We suggest that the appearance of the plateau waves in continuous ICP recording is an important sign indicating an impairment of CSF absorption capacity and a marked sluggishness in CSF flow.

REFERENCES

Børgesen SE, Gjerris F, Sørensen SC (1978) The resistance to cerebrospinal fluid absorption in humans. *Acta Neurologica Scandinavia*, **57**, 88–96.

Børgesen SE, Gjerris F, Sørensen SC (1979) Intracranial pressure and conductance to outflow of cerebrospinal fluid in normal-pressure hydrocephalus. *Journal of Neurosurgery*, **50**, 489–493.

Crevel H van (1979) Papilloedema, CSF pressure, anda CSF flow in cerebral tumours. *Journal of Neurology, Neurosurgery, and Psychiatry*, **42**, 493–500.

Curl FD, Harbert JC, McCullough DC (1972) Quantitative cisternography: an aid to diagnosis. In: *Cisternography and Hydrocephalus*. Edited by J. C. Harbert. Springfield: Charles C. Thomas, pp. 441–451.

Cutler RWP, Page L, Galicich J, Watters GV (1968) Formation and absorption of cerebrospinal fluid in man. *Brain*, **91**, 707–720.

Ekstedt J (1978) CSF hydrodynamic studies in man. *Journal of Neurology, Neurosurgery, and Psychiatry*, **41**, 345–353.

Gjerris F, Børgesen SE, Hoppe E, Boesen F, Nordenbo AM (1982) The conductance to outflow of CSF in adults with high-pressure hydrocephalus *Acta Neurochirurgica*, **64**, 59–67.

Gjerris F, Sørensen PS, Vorstrup P, Paulson OB (1985) Intracranial pressure, conductance to cerebrospinal fluid outflow, and cerebral blood flow in patients with benign intracranial hypertension (pseudotumor cerebri). *Annals of Neurology*, **17**, 158–162.

Hansen K, Gjerris F, Sørensen PS (1987) Absence of hydrocephalus in spite of impaired cerebrospinal fluid absorption and severe intracranial hypertension. *Acta Neurochirurgica*, **86**, 93–97.

Hayashi M, Kobayashi H, Fujii H, Yamamoto S (1982) Ventricular size and isotope cisternography in patients with acute transient rises of intracranial pressure (plateau waves). *Journal of Neurosurgery*, **57**, 797–803.

Hayashi M, Kobayashi H, Kawano H, Handa Y, Kabuto M, Noguchi I *et al.* (1986) Isotope cisternography in patients with intracranial hypertension. *Journal of Nuclear Medicine*, **27**, 471–477.

Hayashi M, Ishii H, Handa Y, Kobayashi H, Kawano H, Kabuto M (1987) Role of the medulla oblongata in plateau-wave development in dogs. *Journal of Neurosurgery*, **67**, 97–101.

Hunt WE, Hess RM (1968) Surgical risk as related to time of intervention in the repair of intracranial aneurysms. *Journal of Neurosurgery*, **28**, 14–20.

Johnston I, Paterson A (1974) Benign intracranial hypertension: II. CSF pressure and circulation. *Brain*, **97**, 301–312.

Katzman R, Hussey F (1970) A simple constant-infusion manometric test for measurement of CSF absorption: I Rationale and method. *Neurology, Minneapolis*, **20**, 534–544.

Kjällquist Å, Lundberg N, Pontén U (1964) Respiratory and cardiovascular changes during rapid spontaneous variations of ventricular fluid pressure in patients with intracranial hypertension. *Acta Neurologica Scandinavica*, **40**, 291–317.

Lorenzo AV, Page LK, Watters GV (1970) Relationship between cerebrospinal fluid formation, absorption and pressure in human hydrocephalus. *Brain*, **93**, 679–692.

Lundberg N (1960) Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatrica et Neurologica Scandinavica*, **36**, Supplement 149, 1–193.

Lundberg N, Cronqvist S, Kjällquist Å (1968) Clinical investigations on interrelations between intracranial pressure and intracranial hemodynamics. *Progress in Brain Research*, **30**, 69–75.

Lundberg N, Kjällquist Å, Kullberg G, Pontén U, Sundberg G (1974) Nonoperative management of intracranial hypertension. In: *Advances and Technical Standards in Neurosurgery*, Volume 1. Edited by H. Krayenbühl. Vienna: Springer, pp. 3–59.

Masserman JH (1934) Cerebrospinal hydrodynamics: IV. Clinical experimental studies. *Archives of Neurology and Psychiatry, Chicago*, **32**, 523–553.

Penning L, Front D (1975) The abnormal scinticisternogram. In: *Brain Scintigraphy: A Neuroradiological Approach*. Edited by L. Penning and D. Front Amsterdam: Excerpta Medica, pp. 287–303.

RISBERG J, LUNDBERG N, INGVAR DH (1969) Regional cerebral blood volume during acute transient rises of the intracranial pressure (plateau waves). *Journal of Neurosurgery*, **31**, 303–310.

RUBIN RC, HENDERSON ES, OMMAYA AK, WALKER MD, RALL DP (1966) The production of cerebrospinal fluid in man and its modification by acetazolamide. *Journal of Neurosurgery*, **25**, 430–436.

SCHLESINGER EB, BAILEY S, GROOVER R (1965) Patterns of central nervous system pathology as depicted by isotope encephalography. *Transactions of the American Neurological Association*, **90**, 292–294.

SKLAR FH, BEYER CW, RAMANATHAN M, COOPER PR, CLARK WK (1979) Cerebrospinal fluid dynamics in patients with pseudotumor cerebri. *Neurosurgery*, **5**, 208–216.

VASSILOUTHIS J, RICHARDSON AE (1979) Ventricular dilatation and communicating hydrocephalus following spontaneous subarachnoid hemorrhage. *Journal of Neurosurgery*, **51**, 341–351

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Brain (1991), **114**, 2693–2699

PLATEAU-WAVE PHENOMENON (II)

OCCURRENCE OF BRAIN HERNIATION IN PATIENTS WITH AND WITHOUT PLATEAU WAVES

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SUMMARY

From 1980 to 1989, during intracranial pressure (ICP) recording, brain herniation (central transtentorial herniation associated with uncal herniation) developed in 15 patients as a result of aneurysmal rebleeding, uncontrollable brain swelling and/or oedema in spite of attempts at treating increased ICP. The relationship between the ICP level at which herniation occurred and the ICP fluctuation patterns in continuous ICP recordings prior to the development of the herniation was studied retrospectively. As for the ICP fluctuation patterns, the patients were assigned to 2 groups on the basis of the presence or abscence of plateau waves of Lundberg: group I comprising 8 patients without plateau waves but with a high ICP, and group II comprising 7 patients with both plateau waves and a high ICP. In the group I patients the herniation occurred as a result of aneurysmal rebleeding or brain swelling after subarachnoid haemorrhage, and in the group II patients the herniation resulted from brain tumour, meningitis carcinomatosa and superior sagittal sinus thrombosis. In the group I patients the herniation developed at a mean ICP level of 70–98 mmHg, and in the group II patients it occurred at a mean ICP level of 120–150 mmHg, far higher than the ICP level causing herniation in the group I patients. It has been shown that patients with a plateau-wave phenomenon in continuous ICP recordings have a marked impairment of cerebrospinal fluid (CSF) absorption and a delayed CSF flow. We suggest that the group II patients have an impairment of CSF absorption and a markedly sluggish CSF flow, and this condition produces a large accumulation of CSF either in the cranial or in the spinal canal cavities, creating a critically taut condition in which pressure gradients can no longer be permitted within these cavities, and which act as a defence mechanism against the herniation, despite the marked increase in the ICP.

INTRODUCTION

The most serious complication in patients with intracranial hypertension is brain herniation. Plum and Posner (1972) have categorized 3 major patterns of supratentorial brain shifts in patients with increased intracranial pressure (ICP): cingulate herniation under the falx cerebri, central transtentorial herniation through the tentorial opening, and uncal herniation over the lateral edge of the tentorium. Of these brain shifts, the central transtentorial herniation is of a life-threatening nature, causing coma, decerebrate posture and other clinical signs.

From 1980 to 1989, ICP has been monitored continuously in 109 patients with increased ICP. During the ICP recording, however, central transtentorial herniation associated

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with uncal herniation developed in 15 patients as a result of aneurysmal rebleeding, uncontrollable brain swelling and/or oedema due to severe subarachnoid haemorrhage, brain tumour, superior sagittal sinus thrombosis and meningitis carcinomatosa in spite of several attempts at treating increased ICP. In this study, we have retrospectively analysed these patients' ICP traces before development of the brain herniation and attempted to clarify whether there is a relationship between the ICP fluctuation patterns and the ICP level at which the herniation occurred.

SUBJECTS AND METHODS

Patients

We have studied 15 patients who developed central transtentorial herniation during ICP monitoring. Nine were males and 6 were females. Their ages ranged from 32 to 58 yrs, with a mean age of 47 yrs. The diagnoses, signs of herniation, causes of herniation and range of mean ICP level at the time of herniation are given in Tables 1 and 2. Patients are grouped according to the ICP monitoring patterns before development of the herniation: group I comprising 8 patients with an ICP pattern of only rhythmic waves (Table I), and group II consisting of 7 patients with an ICP pattern of both plateau waves and rhythmic waves or only plateau waves (Table 2). Written informed consent was obtained from each family (and/or patient, if possible) prior to the study.

ICP recordings

The ICP recording method was based on that described by Lundberg (1960), and is described in the previous paper (Hayashi *et al.*, 1991).

The mean ICP was calculated as the diastolic pressure plus one-third of the pulse pressure. Pressure waves, that is, the ICP irregularities, were defined according to Lundberg's description (1960). Rhythmic waves in the ICP were identified as oscillations with a frequency of 2.5 per min (B-waves), and with a frequency of 4–8 per min (C-waves). Plateau waves recurred at intervals of varying length.

All the patients with increased ICP in this study were treated by intubation and hyperventilation, the administration of both osmotic agents, such as mannitol or glycerol, and steroids. Continuous ventricular drainage was also carried out in all patients prior to or just after the herniation, but the procedure was ineffective because the drainage tube was filled with clots or small tumour masses in patients with ruptured aneurysm and meningitis carcinomatosa, and in other patients, the ventricles became slit-like or shifted laterally and the tube could no longer drain the CSF.

RESULTS

In the group I patients the herniation signs occurred at a mean ICP level of between 70 and 98 mmHg due to aneurysmal rebleeding or brain swelling (Table 1). Fig. 1 is an ICP recording in a group I patient (Case 5 in Table 1). This patient's condition at the time of admission was grade IV on Hunt and Hess' grading system (1968). Continuous ventricular drainage was carried out immediately after admission to improve the patient's condition. Three hours after the procedure, however, the ICP showed a steep rise to about 78–88 mmHg after the intracranial aneurysmal re-rupture, and the patient suddenly became comatosed and exhibited anisocoria.

In the group II patients, on the other hand, the signs of herniation appeared at a mean ICP level of between 120 and 150 mmHg as a result of uncontrollable brain swelling (Table 2). This ICP level was far higher than the mean ICP level causing the herniation in the group I patients. Moreover, in group II, patients were drowsy or almost fully conscious when the mean ICP increased to between 70 and 90 mmHg during the plateau

TABLE 1. PATIENTS WHO DEVELOPED BRAIN HERNIATION DURING ICP RECORDING IN GROUP I

Case no.	*Age (yrs), sex*	*Diagnosis*	*Herniation signs*	*Cause of herniation*	*Range of mean ICP levels at time of herniation (mmHg)*
1	43, M	SAH (rupture of aneurysm ICA)	Coma, decerebrate rigidity, dilated and fixed pupils	Rebleeding	78–86
2	52, F	SAH (rupture of aneurysm: ICA)	Coma, dilated and fixed pupils	Brain swelling	70–96
3	43, M	SAH (rupture of aneurysm: ICA)	Coma, dilated and fixed pupils	Rebleeding	80–98
4	49, M	SAH (rupture of aneurysm: ACoA)	Coma, dilated and fixed pupils	Rebleeding	86–93
5	38, M	SAH (rupture of aneurysm: ICA)	Coma, decerebrate posture dilated and fixed pupils	Rebleeding	78–88
6	59, F	SAH (rupture of aneurysm: ACoA)	Coma, anisocoria	Brain swelling	76–84
7	49, F	SAH (rupture of aneurysm: ACoA)	Coma, decerebrate posture, anisocoria	Brain swelling	78–96
8	49, M	SAH (rupture of aneurysm: VBA)	Coma, decerebrate posture, anisocoria	Brain swelling	82–90

ICP = intracranial pressure; SAH = subarachnoid haemorrhage, ICA = internal carotid artery; ACoA = anterior communicating artery; VBA = vertebrobasilar artery.

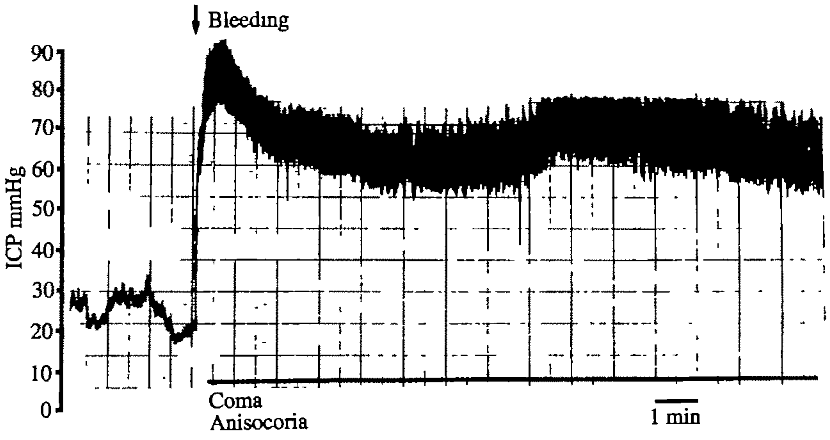

FIG 1 Case 5 in Table 1. Recording of intracranial pressure (ICP) during rupture of the intracranial aneurysm. Coma and anisocoria developed when the mean ICP level was in the range of 78–88 mmHg

waves. This ICP level, however, was invariably associated with herniation in the group I patients. Fig. 2 shows an ICP recording in a group II patient (Case 2 in Table 2). The patient developed coma, decerebrate posture and aniscoria when the mean ICP exceeded 135 mmHg. In this patient the administration of glycerol and steroids, and intubation and hyperventilation were carried out; from this time the mean ICP was about 60 mmHg. In spite of these treatments severe brain swelling progressed and herniation occurred.

DISCUSSION

Plum and Posner (1972) claimed that central transtentorial herniation of the diencephalon is the end result of downward displacement of the hemispheres and the basal nuclei, compressing and eventually displacing the diencephalon and the adjoining midbrain caudally through the tentorial notch. Bruce (1986) suggested that herniation

TABLE 2 PATIENTS WHO DEVELOPED BRAIN HERNIATION DURING ICP RECORDING IN GROUP II

Case no.	*Age (yrs), sex*	*Diagnosis*	*Herniation signs*	*Cause of herniation*	*Range of mean ICP levels at time of herniation (mmHg)*
1	32, M	Metastatic tumour (rt occipital)	Coma, anisocoria	Brain swelling and/or oedema	126–145
2	58, F	Superior sagittal sinus thrombosis due to neoplastic involvement	Coma, decerebrate posture, anisocoria	Brain swelling and/or oedema	135–150
3	43, F	Superior sagittal sinus thrombosis	Coma, anisocoria	Brain swelling and/or oedema	120–138
4	49, M	Glioblastoma multiforme (lt fronto-temporal)	Coma, anisocoria	Brain swelling and/or oedema	122–143
5	42, M	Metastatic tumour (rt fronto-temporal)	Coma, anisocoria	Brain swelling and/or oedema	130–148
6	49, F	Meningitis carcinomatosa	Coma, decerebrate posture, fixed and dilated pupils	Brain swelling and/or oedema	125–148
7	58, M	Meningitis carcinomatosa	Coma, anisocoria	Brain swelling and/or oedema	126–146

ICP = intracranial pressure.

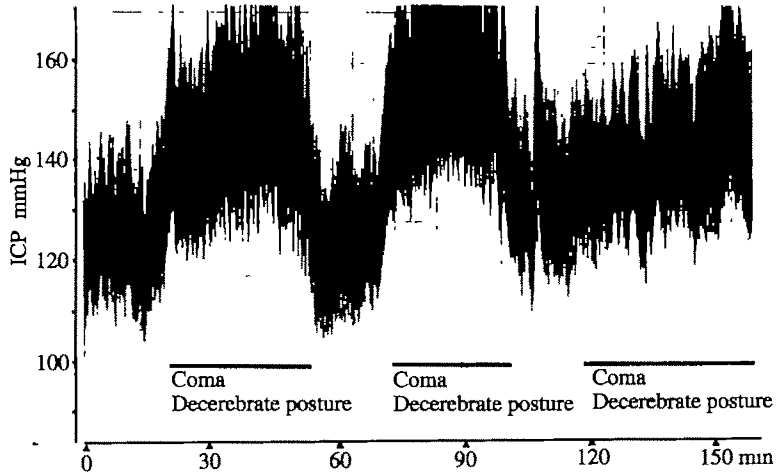

FIG. 2. Case 2 in Table 2 Recording of intracranial pressure (ICP), showing large-amplitude plateau waves Patient developed coma, decerebrate posture, and anisocoria when the mean ICP exceeded 135 mmHg.

syndromes may be due to pressure gradients within the intracranial space, and if the pressure gradient is enough to produce displacement of the cerebral tissue, progressive herniation may occur in the absence of a significantly elevated ICP. It has also been suggested that, clinically, a shift of the brainstem due to central herniation occurs mainly in response to parenchymal lesions of the frontal, parietal and occipital lobes and to extracerebral lesions lying more toward the vertex or the frontal-occipital poles (Plum and Posner, 1972). Clinicopathological observations have suggested that, because the basilar artery is attached to the circle of Willis and cannot move downward, herniation across the tentorium stretches and ruptures the medial perforating branches of the basilar artery and produces brainstem ischaemia and haemorrhages (Johnson and Yates, 1956*a*,*b*; Plum and Posner, 1972; Ropper, 1986). However, the ICP level at which the herniation develops is still a matter of controversy. In this study, the herniation syndromes were not studied with respect to the cause or site of the brain lesions, but were analysed with regard to the ICP levels and ICP fluctuation patterns.

There are several mechanisms that compensate for an increase in ICP, such as shifts of the brain tissue, movement of CSF into the spinal subarachnoid space, increased absorption of CSF, and squeezing of the blood from the cerebral vascular bed (Ryder *et al.*, 1953; Martins *et al.*, 1972; Lundberg *et al.*, 1974; Ropper, 1986). If the limits of these compensatory mechanisms are exceeded, the ICP begins to increase, first slowly (the period of spatial compensation), then more rapidly (the period of spatial decompensation), as the volume of space-taking lesions, intracranial blood or CSF increases (Langfitt *et al.*, 1966; Löfgren *et al.*, 1973; Ropper, 1986). Löfgren *et al.* (1973) observed that, when the ICP increases, the spatial compensation may be mainly due to expansion of the spinal dural sac and to compression of the cerebral venous bed. Lundberg *et al.* (1974) also suggested that, although the reactive ability of the cerebral vessels may manifest as vasoconstriction and squeezing of the blood from the cerebral vascular bed during the period of spatial compensation, if the ICP is on the steep part of the pressure-volume curve, the capacity for mechanical compensation may be exhausted, and vasodilatation elicited by the rise of ICP may develop. In the present study, in the group II patients the signs of herniation developed at a mean ICP level of 120–150 mmHg, far higher than the ICP level of 70–98 mmHg that caused herniation in the group I patients. Also, the high ICP level invariably caused herniation in the group I patients.

It has been reported that both the blood volume and the blood flow in the brainstem maintains a stable level in spite of a marked increase in the ICP during the plateau waves (Hayashi *et al.*, 1985). The present study confirmed this finding: the group II patients showed only drowsiness or were almost fully conscious in spite of a marked increase in the ICP to levels of between 70 and 90 mmHg during the plateau waves.

We have no clear explanation for the big difference of the mean ICP level causing herniation between the two groups. It has been shown that the patients without plateau waves in their continuous ICP recordings had neither a delay nor an impairment of CSF absorption in spite of the presence of high ICP, whereas those with plateau waves in the continuous ICP recordings had a marked sluggishness of CSF flow and impaired absorption of the CSF (Hayashi *et al.*, 1982, 1986, 1991). We therefore speculate that the group II patients had a marked impairment of CSF absorption capacity, and a sluggish CSF circulation, and that this condition produced a large accumulation of CSF in either the cranial or the spinal canal cavities, creating a critically taut condition in which pressure gradients within these cavities were no longer possible. We suggest that the condition does not permit a downward displacement of the brainstem, that is, a central transtentorial herniation, and acts as a defence mechanism against herniation despite a marked increase in the ICP.

REFERENCES

Bruce DA (1986) Pathophysiology of intracranial pressure. In: *Diseases of the Nervous System,* Volume II. Edited by A. K. Asbury, G. M. McKhann and W. I. McDonald. Philadelphia: W. B. Saunders and London: William Heinemann, pp. 1044–1052.

Hayashi M, Kobayashi H, Fujii H, Yamamoto S (1982) Ventricular size and isotope cisternography in patients with acute transient rises of intracranial pressure (plateau waves). *Journal of Neurosurgery,* **57,** 797–803.

Hayashi M, Kobayashi H, Handa Y, Kawano H, Kabuto M (1985) Brain blood volume and blood flow in patients with plateau waves. *Journal of Neurosurgery,* **63,** 556–561.

Hayashi M, Kobayashi J, Kawano H, Handa Y, Kabuto M, Noguchi Y, Shirasaki N (1986) Isotope cisternography in patients with intracranial hypertension. *Journal of Nuclear Medicine,* **27,** 471–477.

Hayashi M, Handa Y, Kobayashi H, Kawano H, Ishii H, Hirose S (1991) Plaeau-wave phenomenon (I). Correlation between the appearance of plateau waves and CSF circulation in patients with intracranial hypertension. *Brain,* **114,** 2681–2691.

Hunt WE, Hess RM (1968) Surgical risk as related to time of intervention in the repair of intercranial aneurysms. *Journal of Neurosurgery,* **28,** 14–20.

Johnson RT, Yates PO (1956*a*) Clinico-pathological aspects of pressure changes at the tentorium. *Acta Radiologica,* **46,** 242–249.

Johnson RT, Yates PO (1956*b*) Brain stem haemorrhages in expanding supratentorial conditions. *Acta Radiologica,* **46,** 250–256.

Langfitt TW, Weinstein JD, Kassell NF, Simeone FA (1966) Vascular factors in head injury. In: *Head Injury, Conference Proceedings*. Edited by W. F. Caveness and A. E. Walker. Philadelphia: J. B. Lippincott, pp. 172–194.

Löfgren J, von Essen C, Zwetnow NN (1973) The pressure-volume curve of the cerebrospinal fluid space in dogs. *Acta Neurologica Scandinavica*, **49**, 557–574.

Lundberg N (1960) Continuous recording and control of ventricular fluid pressure in neurosurgical practice. *Acta Psychiatrica et Neurologica Scandinavica*, **36**, Supplement 149, 1–193.

Lundberg N, Kjällquist Å, Kullberg G, Ponten U, Sundberg G (1974) Non-operative management of intracranial hypertension. In: *Advances and Technical Standards in Neurosurgery*, Volume 1. Edited by H. Krayenbühl. Vienna: Springer, pp. 3–59.

Martins AN, Wiley JK, Myers PW (1972) Dynamics of the cerebrospinal fluid and the spinal dura matter. *Journal of Neurology, Neurosurgery, and Psychiatry*, **35**, 468–473.

Plum F, Posner JB (1972) Supratentorial lesions causing coma. In: *The Diagnosis of Stupor and Coma*. Second edition. Edited by F. Plum and J. B. Posner. Philadelphia: F. A. Davis, pp. 63–118.

Ropper AH (1986) Acute increased intracranial pressure. In: *Diseases of the Nervous System*, Volume II. Edited by A. K. Asbury, G. M. McKhann and W. I. McDonald. Philadelphia: W. B. Saunders and London: William Heinemann, pp. 1064–1073.

Ryder HW, Espey FF, Kimbell FD, Penka EJ, Rosenauer A, Podolsky B *et al.* (1953) The mechanism of the change in cerebrospinal fluid pressure following an induced change in the volume of the fluid space. *Journal of Laboratory and Clinical Medicine*, **41**, 428–435.

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ANNOUNCEMENTS

The following seven courses are being organized by the University of California For further information, please contact Radiology Postgraduate Education, Room C-324, University of California School of Medicine, San Francisco, CA 94143-0628, USA (Tel. 415 476-5731; Fax: 415 476-9213):

Magnetic Resonance Imaging in the Desert, February 3–7, 1992. Ritz-Carlton, Rancho Mirage, California.

Diagnostic Imaging Update 1992. February 16–21, 1992. Shadow Ridge, Park City, Utah.

Head and Neck Imaging: Total Immersion, February 27–29, 1992. Ritz-Carlton, Rancho Mirage, California.

Magnetic Resonance Imaging. Update 1992—Winter Conference, March 8–13, 1992. Mariott's Mark Resort, Vail, Colorado.

The 35th Annual Diagnostic Radiology Postgraduate Course, March 23–27, 1992. Fairmont Hotel, San Francisco, California.

Pediatric Imaging Update, March 30–April 3, 1992. Camelback Inn, Scottsdale, Arizona

Diagnostic Imaging: 1992, April 5–10, 1992 Hyatt Regency, Kanai, Hawaii

The following two courses are being organized by the American Registry of Pathology and the Armed Forces Institute of Pathology at the Hyatt Regency Bethesda, Bethesda, Maryland, USA. For application information for the courses, contact Education Division, Armed Forces Institute of Pathology, Washington DC 20306–6000 (Tel: 301 427-5231)

The Annual AFIP Neuropathology Review Course, February 29–March 1, 1992

The 30th Annual AFIP Neuropathology Review Course, March 2–6, 1992.

The following two courses are being organized by the New York Academy of Sciences. For further information, contact the Conference Department, New York Academy of Science, 2 East 63rd Street, New York, NY 10021 (Tel: 212 838-0230; Fax· 212 888-2894)

Myasthenia Gravis and Related Disorders. Experimental and Clinical Aspects Hyatt Regency Washington on Capital Hill, Washington DC, USA, April 12–15, 1992.

The Neurohypophysis: a Window on Brain Function, Dartmouth College, Hanover, New Hampshire, USA, July 16–20, 1992.

The following two courses are being organized by the Institute of Psychiatry (University of London), the Mandsley Hospital and Bethlem Royal Hospital. For information, contact Mrs Lee Wilding, Conference Office, Institute of Psychiatry, De Crespigny Park, London SE5 8AF (Tel: 071 703 5411, ext. 3170; Fax 071 703 5796).

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Treatment and Care in Old Age Psychiatry, July 8–10, 1992.

The 4th Annual Symposium—Treatment of Headaches and Facial Pain

This symposium will be held at the New York Marriott—East Side in New York City, April 26, 1992. For information, contact Alexander Mauskop, The Downstate Headache Center, 132 Atlantic Avenue, Brooklyn Heights, NY 11201, USA (Tel: 718 935-9666).

The 11th Annual Scientific Meeting and Exhibition of the Society of Magnetic Resonance in Medicine

This meeting will be held in Berlin, Germany, August 8–14, 1992 For information, contact SMRM, 1918 University Avenue, Suite 3C, Berkeley, CA 94704, USA (Tel: 510 841-1899; Fax 510 841-2340).

Ultrasound Angiography 92—2nd International Conference

This conference will be held in the Medical and Biological Sciences Building, University of Southampton, UK, September 2–4, 1992. For further information, contact Conference Secretariat, Ultrasound Angiography 92, PO Box 15, Eastleigh, Hampshire SO5 5XG, UK.

International Congress on Objective Assessment in Rehabilitation Medicine—Low Back Pain and Brain Injury

This congress will be held in Montréal, Québec, Canada, October 5–6, 1992. For information, contact Centre de formation en réadaptation du Québec, 6300, Avenue Darlington, Montréal, Québec, Canada H3S 2J4 (Tel: 514 340-2089, Fax: 514 340-2149).

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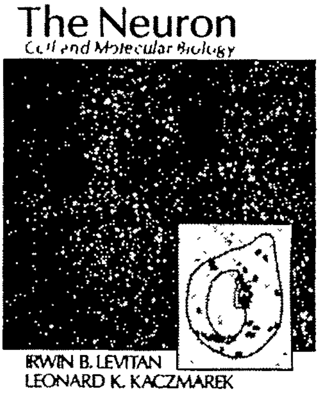

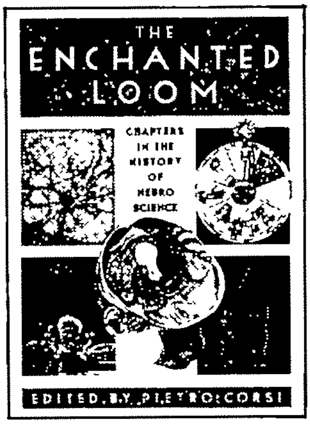

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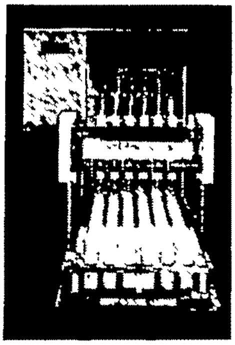

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